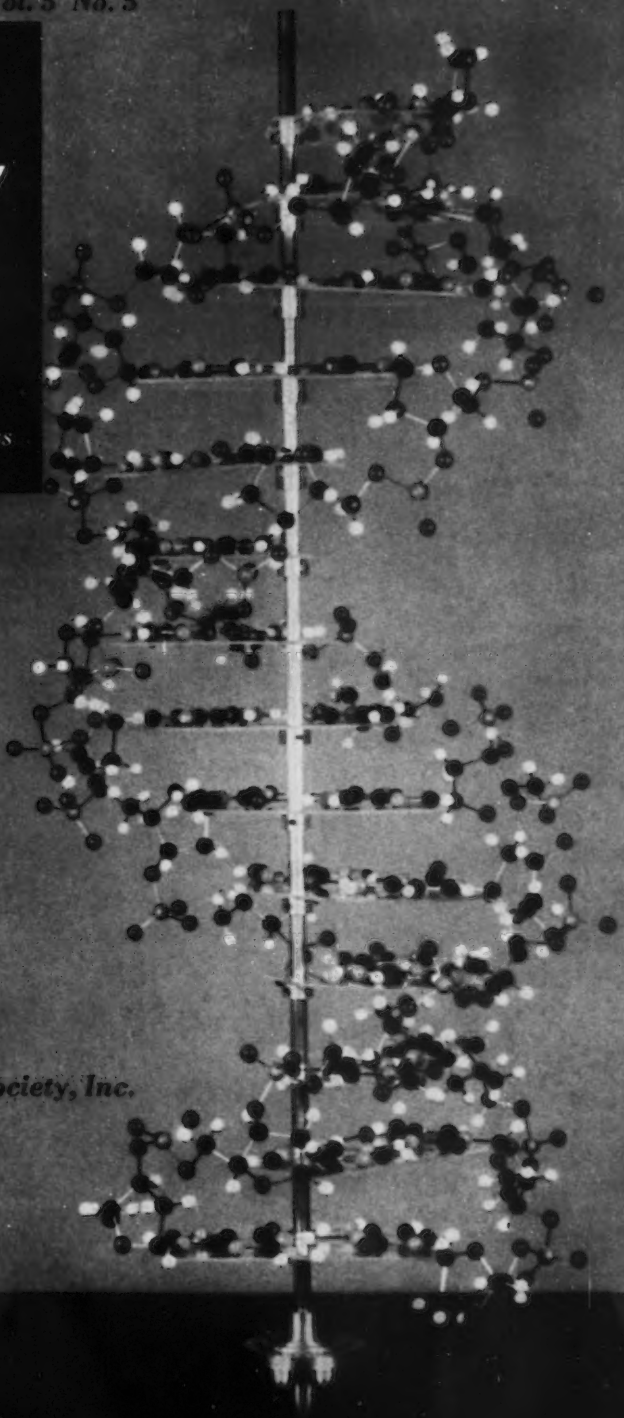
September 1955 Vol. 5 No. 5

Ca

a Bulletin of Cancer Progress



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DNA fabric of the gene

As revolutionary discoveries in nuclear physics have been of importance in the radiation treatment of cancer, so advances in our knowledge of nucleic acids hold promise for the chemotherapy of cancer and for new research in this area.

There are two types of nucleic acid, pentosenucleic acid (PNA) and deoxyribosenucleic acid (DNA). DNA is found in all living cells with the exception of a few viruses which contain its close relative, PNA. In plants and animals, all the DNA is in the nucleus, localized in the chromosomes—the gene carriers. Many lines of evidence indicate that DNA is the actual genetic material.

The chemistry of the building blocks of DNA is now well known. Many of the chemotherapeutic agents now in use for the palliation of certain cancers exert their main effect by interfering with the synthesis of one or another building block of nucleic acid.

In the past two years accurate three-dimensional models of DNA have been conceived and tested. This long-sought goal was neared through the x-ray–diffraction work of Wilkins and others at the Medical Research Council, Biophysics Unit, King's College, London. They found that DNA yields a picture that indicates a remarkably regular—even crystalline—structure, which indicates that this giant molecule has a simple repeating basic pattern. There was no difference in the patterns of crystalline DNA obtained from numerous species, including normal and leukemic human leukocytes, although the ratios of the nitrogenous components in the DNA's differed. The simplifying concept of the specific pairing of nitrogenous components suggested by Watson and Crick of the MRC Unit, Cavendish Laboratory, Cambridge, England, neatly coordinated these observations.

The model on the cover provides a geometry for the duplication of genes in cell division and for the organization of new chromosomes; it shows a pair of deoxyribose-phosphate chains wound in a double helix. The helical chains are held together by closely fitting pairs of nitrogenous bases: adenine and thymine, guanine and cytosine.

The linear sequences of the pairs of bases are not known, but one hypothesis is that these sequences act as a genetic code much as the sequence of information on tape fed into a computer. In a single human chromosome, the DNA stretched out as single fiber on the scale of this model would extend from New York to Rome; there would be a pair of bases every 6.8 cm. of the way, and so such a code could carry all the information required to account for the events of heredity.

This deeper chemical explanation for inheritance should also deepen our understanding of the causes of cancer. But just as knowledge of the chemical formulas of the small building blocks of DNA has enlightened empiricism in cancer chemotherapy and has led to the discovery of clinically useful chemical agents, so it may be expected that knowledge of the macromolecular structure of DNA will encourage the design of larger antimetabolite units. The transforming activity of bacterial DNA gives a clue that in bacteria, at least, relatively large macromolecules are biologically active and probably function as a unit. So far experiments have not succeeded in detecting genetical transformation with DNA in organisms other than bacteria. Do such transformations occur in higher organisms? Is it too much to hope that, in the future, transformation of cancer cells into normal cells may be achieved by treament with appropriate DNA's?

Cover—
Early model of the proposed structure of deoxyribosenucleic acid *B*.

NEWSLETTER

SEPTEMBER, 1955

An interesting assault against a transplanted mouse lymphoma has been made from two quarters -- by Kidd (Cornell U.) and by Bahner (Carson-Newman) in collaboration with Wistar and U. of Pennsylvania investigators. Kidd has completely destroyed the tumors with large quantities of guinea-pig serum, and the Carson-Newman and Philadelphia groups have obtained repeated and presumably complete regressions with styryl quinolines.

Kidd's results were limited in scope. Guinea-pig serum, while it erased these tumors completely even when given fairly late in the course of the disease, has failed to affect several other tumors on which it was tested. And serum from a dozen other species, including the human, has had no effect on the lymphoma. The Cornell scientist is now trying to identify the carcinolytic factor in guinea-pig serum and to determine whether it will have a synergistic effect when used in combination with other agents.

The Carson-Newman--Philadelphia group's results were equally spectacular. When the styryl quinolines were fed to mice with large tumor masses, the tumors disappeared -- and they left in their wake neither necrotic tissue nor hemorrhage. If metastases brought about a recurrence of the disease, another course of styryl quinoline (it is given with food) for ten days resulted in complete regression of the new tumors. The group has not reported whether the compounds are effective against other kinds of experimental cancers. Neither the serum nor the styryl quinolines showed marked toxicity.

Touster (Vanderbilt U.) is developing techniques to trace lost or strayed glucuronides. Others have reported that the human body -- chiefly the liver -- produces about a half gram of glucuronic acid daily. Touster and others have been able to find less than one tenth that amount in excretion studies. Glucuronides are believed to detoxify excess steroids, alcohol, phenols, and a number of drugs, including sulfonamides and aspirin, by binding with them.

Perhaps in retrospect we shall recognize this as a year in which significant advances were made in protein chemistry.

Smith and Kimmel (U. of Utah) have made considerable progress in breaking up and analyzing the enzyme papain, which is about 180 amino acids long. They use carboxypeptidase to clip amino acids, one at a time, off one end of the chain and aminopeptidase to clip them off the other end. They also use trypsin to split the chain into natural segments at lysine and arginine couplings. They have determined that the papain molecule loses none of its activity after having been shorn of at least nineteen amino acids. They are whittling the active fraction down to even smaller size and determining the order of the amino acids as they come off the terminals.

Neurath (U. of Wash.) has learned how some inactive proenzymes become active enzymes. He and associates (Bettelheim of Cambridge, Davis of Harvard, and Dreyer of Wash.) have noted that the six terminal amino acids of trypsinogen "stick out of the protein molecule like a sore thumb." When these are sheared off by trypsin, the trypsinogen becomes more trypsin. Neurath has determined that calcium ions mus' be present to transform trypsinogen into trypsin. With Vallee (M.I.T.), Neurath has found that carboxypeptidase contains zinc, and the two scientists are trying to find out what role the zinc plays. Neurath and his associates also have learned that chymotrypsinogen is converted to active chymotrypsin when, in a series of steps, trypsin breaks a single one of the 300 peptide bonds in the proenzyme -- one linking leucine and arginine. The breaking of this single bond starts a series of reactions in which various degraded (pi, alpha, beta, gamma, etc.) chymotrypsins act upon themselves. All forms are biologically active but differ from each other in the groups that form the terminals of the polypeptide chain.

One of the potential clinical advantages of current protein work such as this is the extraction of active fractions of enzymes and other proteins and the analysis and synthesis of polypeptide drugs. This may herald in an age of miracle medicine now impossible to envision.

Waisman (U. of Wis.), in the course of an extensive study of blood and urine proteins of cancer patients, has come up with a remarkable preliminary finding. He has found

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Keeping up

Hysterectomy and Pelvic Lymphadenectomy

A group of 473 cases of cancer of the uterus, vagina, and cervix treated by radical hysterectomy and pelvic lymphadenectomy at Vincent Memorial, Pondville, Palmer Memorial, and Massachusetts General hospitals during a fifteen-year period, 1939 to 1953, is analyzed from the standpoint of certain clinical aspects and results of treatment. Of the 473 cases operated upon, 244 operations were for primary invasive carcinoma of the cervix. Primary squamous-cell carcinoma was by far the most frequent type in this group. The patients' ages ranged from 17 to 80 years, with the peak in the late forties. Twenty-four were unmarried; 449 were married, 47 per cent before the age of 20. Nine of the 397 with cancer of the cervix were single. Symptoms varied from no complaints or oligomenorrhea for six months to intermittent vaginal bleeding for eleven years. Parity ranged from primary sterility to gravida xvii, para xv. Obesity, hypertension, and diabetes were the most frequent concurrent constitutional diseases. Six of the entire group were pregnant at the time of operation and are all well three to eleven years later. Multiple cancer existed in 5 per cent of the entire group; 19 per cent gave histories of cancer in one or more members of their families. Oophorectomy had been performed in twenty-eight and roentgen-ray castration in nine, from four to thirty-four years previously. Nine per cent developed fistulas, the most frequent operative complication. Pelvic hematomas and abscesses were the next most frequent complications. Twenty-nine per cent had received preoperative irradiation (1) as initial treatment of choice, (2) as preliminary to surgical treatment, or (3) as combined treatment. In 25 per cent, lymph-node metastases were present, the obturator group being the most frequently involved. The aortic nodes were involved in but two cases. Surgical mortality was 1.7 per cent. There was but one operative death among 344 cases of primary cervical cancer. One hundred of the 473 patients died, one third in the first year. Of the patients not surviving five years, 85 per cent died within three and one-half years. The five-year–salvage rates in 193 patients with carcinoma of the cervix were: Stage I, 75 per cent; Stage II, 54 per cent. In the forty-nine cases with lymph-node metastases the salvage rate was 35 per cent and in the 144 cases without lymph-node metastases, 81 per cent.

Liu, W., and Meigs, J. V.: Radical hysterectomy and pelvic lymphadenectomy; a review of 473 cases including 244 for primary invasive carcinoma of the cervix. Am. J. Obst. & Gynec. 69: 1-32, Jan., 1955.

Survival after Lung-Cancer Surgery

In 689 thoracotomies, at Middlesex, London Chest, and Harefield hospitals, from 1940 to 1950, 446 tumors were found suitable for excision—a two-thirds operability rate. Follow-up in 1953 of the group operated on prior to 1948 (273 cases) showed a survival rate of 34 per cent at the end of two years; 30 per cent, at three years; 23.5 per cent, at four years; and 21 per cent at five years. In the 1949–1950 series (173 cases) 40 per cent were

with Cancer

alive at the end of two years and 34 per cent at three years. Pneumonectomy is now the standard operation for pulmonary cancer, although more limited resections are possible in certain circumstances. Improvements in all branches of thoracic medicine and surgery have made the required technical procedures relatively safe for all cases in which the tumor mass can be removed and in which the patient can sustain the loss of lung tissue. The most obvious contraindication is the patient's inability to withstand removal of the lung tissue—a rigid chest, gross emphysema, chronic bronchitis, and persistent bronchospasm. Age alone is not a serious hazard.

Sellors, T. H.: Results of surgical treatment of carcinoma of the lung. Brit. M. J. 1: 445-448, Feb. 19, 1955.

Cancer of the Male Breast

About 1 per cent of carcinomas of the breast occur in males. In the seventy-five cases (fifty primary) reviewed, the median age was 64 years—distinctly higher than in female cases. Four and one-half months was the median time elapsed before seeking therapy. The usual initial symptom was an asymptomatic nodule in the breast. In one patient the initial symptom was bleeding from the nipple; in another, retraction of the nipple; and in another, pain. Pain was a prominent symptom later in the course of the disease. Seventy-two per cent of the patients had axillary lymph-node involvement on initial examination. Metastatic sites do not differ materially from those of female breast cancer. The five-year–cure rate for primary cases was 12 per cent. No case with skin ulceration or the slightest pectoral invasion was cured. Hormone therapy should not replace radical mastectomy in the favorable cases but is of distinct value in prolonging useful life. Orchiectomy initially gives best results. Various estrogens and even testosterone were used in selected cases. Bilateral adrenalectomy is to be employed after all other palliative procedures have failed.

Huggins, C., Jr., and Taylor, G. W.: Carcinoma of male breast. A.M.A. Arch. Surg. 70: 303-308, Feb., 1955.

Cancer of the Stomach

Material of the Ochsner Clinic is reviewed and compared with that of other clinics. Forty thousand deaths from cancer of the stomach occur annually—53.7 deaths per 100,000 population in 1953, compared with 17.9 in 1948. One of every 588 admissions to the Ochsner Clinic had gastric cancer, one in 200 at the Mayo Clinic, and one in 265 at the Charity Hospital in New Orleans. For so common a lesion the diagnosis and treatment are far from satisfactory, largely because of lack of early diagnosis. Every patient past 40 years of age with gastric symptoms that cannot be explained otherwise should be suspected of having gastric cancer. The operability rate varies from 50 to 88.9 per cent in different institutions, and resectability from 25 to 54 per cent. The lesion was apparently limited to the stomach in but 12.5 per cent of Ochsner's series. The five-year–survival rate varies from 5 to 14

per cent. Total gastrectomy is recommended for proximal lesions and radical subtotal resection for distal lesions. Poor results in the management of gastric cancer indicate the necessity for earlier diagnosis rather than for more radical procedures. All patients with chronic gastric ulcers, gastric polyps, and certain forms of persistent gastritis should be subjected to gastric resection. Abdominal exploration is recommended in men past 40 years with gastric symptoms and weight loss not responding to therapy.

Ochsner, A.; Blalock, J., and Sucre, A.: Carcinoma of the stomach. Am. Surgeon 21: 1-16, Jan., 1955.

Transmitted Radiation Effects

Analysis of a questionnaire answered by several thousand male radiologists and several thousand nonradiologist physicians concerning their offspring showed a significantly greater incidence of congenital malformations among children of radiologists (about 6 per cent) than of the nonradiologists (about 5 per cent). Among these congenital abnormalities, neoplasms were second only to defects in the sense organs. Of the malformations among the children of the radiologists, 16 per cent were neoplasms, contrasted to 14 per cent among the children of the nonradiologists. More than half the neoplasms in both groups were hemangiomas. These small, first-generation differences are considered by the author to represent but a small fraction of the total damage that may be caused by long exposure to radiation.

Macht, S. H., and Lawrence, P. S.: National survey of congenital malformations resulting from exposure to roentgen radiation. Am. J. Roentgenol. 73: 442-466, March, 1955.

Carcinoma of the Gallbladder

Nearly all malignant tumors of the gallbladder are carcinomas. Of 114 carcinomas of the extrahepatic biliary system, including the gallbladder, found in 12,838 necropsies at University of Michigan Hospital, forty-eight were primary to the gallbladder and fifty-eight to the bile ducts, including the ampulla of Vater, and eight were so extensive that the primary site could not be determined. Carcinoma of the gallbladder is twice as common in women as in men, while carcinoma of the extrahepatic ducts is more common in men. In this series calculi were found in 73 per cent of the gallbladder cases but not so frequently in those of carcinoma of the bile ducts. It has long been thought that calculi have a specific carcinogenic effect. For this there is no proof. It is more probable that the sequence is cholecystitis, cholelithiasis, and then carcinoma. In five of the forty-eight cases of carcinoma of the gallbladder there was a second primary carcinoma in the colon, cervix, breast, stomach, or prostate respectively, demonstrating a predisposition to malignant epithelial neoplasms. Moderately well-differentiated adenocarcinomas comprise the bulk of carcinomas of the gallbladder. Scirrhous carcinoma is next in frequency. Sarcoma of the gallbladder is a curiosity. Carcinoma of the bile ducts is more frequent than carcinoma of the gallbladder.

Abell, M. R.: Diseases of the gallbladder: their nature and classification. Canad. M. J. 72: 565-571, April 15, 1955.

Polyps and Cancer of the Colon

Most carcinomas of the colon originate within polyps. Varying degrees of transformation of polyps in the same colon were demonstrated repeatedly. The authors present, in exhibit form, a study of 1000 male patients admitted for all causes, examined by proctosigmoidoscopy and barium-enema roentgenography. Fifteen per cent of these patients were found to have polyps. Eighty-one (54 per cent) of the polyp-bearing patients showed benign, and seventy (46 per cent) malignant, lesions. Benign and Grade-I adenomatous polyps are treated by proctoscopic or transcolonic excision and fulguration of the base or by colectomy, if multiple or widely spread polyps are present. Polyps of Grade II are treated by radical resection by abdominoperineal or anterior routes. Seventy-five per cent of polyps and carcinomas of the colon are within reach of the proctosigmoidoscope.

Recommendations for control of polyps and carcinoma of the colon are: annual proctosigmoidoscopy for all persons more than 40 years of age; semiannual proctosigmoidoscopy and air-contrast barium-enema roentgenographic examination for all patients with family history or previous diagnosis of polyps and for all persons with lower-bowel symptoms.

Walske, B. R.; Hamilton, J. W., and Kisner, P.: From "benign" polyp to carcinoma. A.M.A. Arch. Surg. 70: 318-322, Feb., 1955.

Cytology in Fundal Carcinoma

Routine cytological examination of the endometrium gives an unduly high percentage of false-negative diagnoses. In an effort to improve the accuracy of cytodiagnosis of the endometrium, the author has substituted a rotating brush for the usual surface-biopsy spatula and the cervical aspirator. Conditions in which false-negative results may be obtained are: stenosis of the cervical canal, as in postmenopausal adenocarcinoma; bleeding or serosanguineous discharge; and recent pelvic examination resulting in mild hemorrhage. The endometrial-brush technique is recommended as a secondary cytological procedure in young women showing abnormal endometrial cells and as a primary procedure in postmenopausal women, with or without bleeding. This office procedure yields results exceeded in accuracy only by actual curettage.

Ayre, J. E.: Rotating endometrial brush: new technic for the diagnosis of fundal carcinoma. Obst. & Gynec. 5: 137-141, Feb., 1955.

Printers' Ink and Lung Cancer

Along with cigarette smoke, automobile exhaust, and industrial smoke, printed material has increased greatly in amount in the past several decades and might, therefore, possibly be an additional contributory factor to the enormous increase in lung cancer. Analysis of the Wiklund report on bronchial carcinoma in Stockholm showed that eight (6.4 per cent) of 125 cases of lung cancer were in printing workers, while only 1.14 per cent of all men older than 40 years working in Stockholm were printing workers. This significant difference, together with the facts that only one of three printing employees were working with printing ink and that all eight of the cases of lung cancer occurred in this group, places printing ink high statistically among the etiological factors of lung cancer. Along with the former Schneeberg and Joachimsthal miners and the workers in the modern chromium industry, printing workers should now be considered particularly susceptible to lung cancer. Frequent roentgen-ray screening of printing workers more than 40 years old is recommended.

Ask-Upmark, E.: Bronchial carcinoma in printing workers. Dis. of Chest 27: 427-435, April, 1955.

Cancer Instruction to Dentists

In 1947 the Council on Dental Education of the American Dental Association, in joint meeting with representatives of the National Cancer Institute, agreed to a program of cancer education in the dental colleges. In 1948 grants were made for integration and improvement of cancer teaching. This program has now been extended to include forty-three dental schools. The new generations of practicing dentists are better equipped for the control of intraoral neoplastic disease through earlier diagnosis and treatment. As a result of this NCI teaching program: 1. There has been expansion of oral-cancer instruction. 2. Increased time is being devoted to cancer in the dental curriculum. 3. There is an increase in clinical material for dental students. 4. There is increased utilization of teaching materials, facilities, and equipment. 5. It has been established that knowledge of cancer is pertinent to dentistry and that the dentist has an important role in control of the disease. 6. There is increased medicodental co-operation. 7. The dental student is being impressed with his responsibility for early detection of oral cancer. 8. Dental teaching personnel is being developed. 9. Establishment of diagnostic biopsy services and

research in dental schools has been stimulated.

Kaiser, R. F.: Results of the cancer teaching program in dental schools. Pub. Health Rep. 70: 35-38, Jan., 1955.

Irradiation of Cervical Cancer

From a group of 142 patients with carcinoma of the cervix treated by radiation during a twenty-year period, 1929 to 1949, at the American Oncologic Hospital, Philadelphia, ninety-eight were followed more than five years. The five-year-survival rates were: over-all, twenty-four; stage I, fifty-three; stage II, forty-six; stage III, thirty-five; and stage IV, 0 per cent. Serious postradiation complications developed in 3.5 per cent. Of the patients, 85 per cent were parous; 33 per cent were less than 40 years of age. Abnormal bleeding was by far the most prominent symptom. Nearly one third of the patients had had previous pelvic surgery. More frequent use of diagnostic curettage and of circular cervical biopsy at the time of pelvic surgery is urged.

Hahn, G. A.: Carcinoma of the cervix uteri treated at the American Oncologic Hospital, 1929 to 1949. Am. J. Obst. & Gynec. 69: 48-58, Jan., 1955.

Lung Cancer

Analysis of 704 private patients with primary bronchogenic carcinoma over a period of eleven years showed no improvement in resectability rates—approximately 20 per cent. Improvement in early diagnosis by roentgenological surveys and periodic physical examination is offset by delay in diagnosis incident to increased use of antibacterial drugs. Of sixty-four patients having pulmonary resection, sixty survived surgery; forty died of metastatic carcinoma and eight of other causes, and twelve are living and well five to ten years after surgery—a salvage rate of 31.2 per cent. The salvage rate of all patients seen with a diagnosis of carcinoma of the lung was but 6.3 per cent. Improvement in surgical salvage depends chiefly upon getting these patients to surgery before the neoplasm has extended beyond the lung. The following suggestions are made to the general practitioner: Consider any pulmonary infiltrate that does not disappear promptly under antibacterial therapy as probably neoplastic. Look for lung cancer in all male patients more than 40 years of age. Make chest roentgenograms a part of every physical examination and encourage adult male patients to have such examinations twice a year. Consider all abnormal lung shadows to be cancer until proved not to be. If diagnosis cannot be made otherwise with certainty, recommend exploratory thoracotomy, the mortality rate of which is less than 1 per cent.

Jones, J. C.; Robinson, J. L., and Meyer, B. W.: Primary bronchogenic carcinoma of lung; statistical study of seven hundred four private patients. A.M.A. Arch. Surg. 70: 265-275, Feb., 1955.

Benzidine Test for Blood

It is claimed that several minor modifications of the well-known benzidine test adapt it to screening for cancer of the uterus, stomach, large bowel, and urinary tract. It has generally been stated that the benzidine and orthotoluidine tests are too sensitive to be useful for routine testing of stools of patients not on meat-free diets and that the guaiac test is satisfactory. It is stated here that the effective filtration of the aqueous fecal mixture eliminates false positives from hemoglobin-containing foods, yet the test is so sensitive as to detect blood in a 1:500,000 dilution and to give a positive reaction with urine, stool, duodenal and vaginal contents, etc., containing but "4 to 6 erythrocytes per high power field."

Levin, M. B.: Benzidine test for blood (Levin-Watt). Am. J. Digest. Dis. 21: 358-362, Dec., 1954.

Cervical Cancer

Results from radiation alone in cancer of the cervix are satisfactory with stage-I involvement. However, with stage-II carcinoma, metastatic pelvic involvement is practically incurable by radiation, and surgical eradication of nodes is necessary. With combined therapy, preoperative radiation is given to destroy microscopic rem-

nants of neoplasm, and surgery is performed for gross removal of lymph nodes and fatty tissues. Initially radium or roentgen-ray therapy is employed. Surgery is done six to eight weeks after radiation. Either ileopelvic lymphadenectomy and colpohysterectomy without excision of parametrial tissue or combined pelvic lymphadenectomy and a Wertheim operation are carried out. The latter method is preferred when radiation therapy is ineffective. With some advanced operable lesions, surgery alone may be required, since a delay of six to eight weeks may permit extension of pelvic node metastasis with subsequent adherence to surrounding tissues. In a group of 102 patients with operable cancer of the cervix treated with combined radiation and surgery, the three-year cure rate was 65 per cent. The surgical mortality rate was approximately 8 per cent. Causes of death included peritonitis, coronary disease, embolism, shock, cardiac arrest, and intestinal obstruction.

Dargent, M., and Guillemin, G.: The treatment of operable cancer of the cervix by the combination of radiation and surgery. Cancer 8:53-58, Jan.-Feb., 1955.

Chorioepithelioma

One case of chorioepithelioma occurs in from 26,000 to 60,000 pregnancies. About a quarter of chorioepitheliomas follow normal pregnancies. However, the usual history is that of hydatidiform mole, ectopic pregnancy, or abortion. Diagnosis is always difficult, since the tumor resembles the trophoblastic tissue of normal pregnancy. The uterus is only slightly enlarged. The tumor is infiltrating and metastasizing with dominance of Langhans and syncytial cells and absence of stroma and villi. The chorionic gonadotropin titer is usually increased. Chorioepithelioma is almost always fatal, although regression of tumor or metastases have been reported from radiation and hysterectomy. Metastases to the lung occur in 80 per cent of cases. Spontaneous regressions are explained on an immunological basis. Attempts to control this condition by pituitary inhibition with estrogens have been discouraging. However, with intensive testosterone propionate therapy (100 mg. daily for nine months) after radical surgery in the case presented, a "cannon ball" lung lesion regressed, and the patient, five years later, is living, well, and apparently free of all metastases. The androgen employed acted not only to correct overproduction of gonadotropin but also to increase protein metabolism and to contribute to the patient's feeling of well-being.

Duffy, B. A.: Recovery from metastatic chorionepitheliomia following surgery and long-term androgen therapy; report of a case. Am. J. Obst. & Gynec. 69: 898-904, April, 1955.

Cancer of the Gallbladder

Only one patient in a group of fifty-two operative cases of carcinoma of the gallbladder is living and well forty months after surgery. The average survival in the fatal cases was 4.9 months. From these discouraging results it is concluded that the only effective means of control of cancer of the gallbladder is prevention by cholecystectomy, whenever feasible, in all patients with cholecystitis or cholelithiasis. The author justifies this recommendation not only in the interest of cancer prevention but also as a prophylactic measure against other possible complications of cholecystitis—infection, perforation, scarring, and cholelithiasis—resulting in increased difficulties of operation, with higher morbidity and mortality. Cholecystectomy is advocated for even "silent stones," since in about 50 per cent of these cases symptoms eventually develop. Results of treatment of biliary disease can best be improved by discouraging the medical treatment of cholelithiasis.

Rivkin, L. M.: Carcinoma of gall bladder; report of fifty-two operative cases and résumé of the literature. A.M.A. Arch. Surg. 70: 128-135, Jan., 1955.

Bronchogenic Carcinoma

A group of 234 consecutive autopsies on cases of bronchogenic carcinoma are reviewed to determine the different clinical types and the most common sites of

metastases. The authors conclude that metastases have played an important role in the treatment of bronchogenic carcinoma since the advent of surgery for this condition. It is noted that no organ or structure in the body escapes metastases. These may occur by any of the established routes: (1) direct extension, (2) lymphogenous dissemination, (3) hematogenous dissemination (including the cerebral veins), (4) direct implantation, and (5) bronchogenic spread. Carcinoma of the lung occurs with almost equal incidence on either side and the simplest classification is (1) epidermoid, (2) adenocarcinoma, and (3) undifferentiated. Combinations of these occur and would be difficult to fit arbitrarily into any particular category. The exact origin or cell derivation of each particular type of bronchogenic carcinoma is not entirely known, but the authors believe that the epidermoid and undifferentiated carcinomas arise from the basal-cell layer and the adenocarcinomas arise from the bronchial glands.

Engelman, R. M., and McNamara, W. L.: Bronchiogenic carcinoma; a statistical review of two hundred and thirty-four autopsies. J. Thoracic Surg. 27:227-237, March, 1954.

Air Pollution and Lung Cancer

Demonstration of carcinogens in the atmosphere and in vehicular sources of pollution; production of skin cancer in mice with pollutants extracted from the atmosphere; the greater incidence of lung cancer in urban than in rural districts; the different rates of increasing incidence of lung cancer; and the presence in the atmosphere of substances, although not themselves carcinogens, that provide the mechanism for activity of known and suspected carcinogens—all point toward air pollution as one possible etiological agent responsible for the increasing frequency of lung cancer. However, application to human subjects of conclusions derived from animal-experimentation data on carcinogens is not warranted. That androgenic, progestational, and adrenocortical, but not estrogenic, hormones are destroyed by three minutes' exposure to a smog containing 4 parts per million of total oxidant may be significant in the study of carcinogenic activity of air pollutants.

Kotin, P., and Falk, H. L.: Air pollution and its effect on health. California Med. 82: 19-24, Jan., 1955.

Diagnosis of Prostatic Cancer

Stilbestrol-induced reductions of acid-phosphatase concentrations in prostatic fluids may indicate carcinomatous involvement of the prostate gland. Stilbestrol in daily doses of 10 mg. was administered for seven days to nine patients with carcinoma of the prostate, to five with chronic prostatitis, to five with benign prostatic hypertrophy, and to four healthy individuals. Only the patients with carcinoma of the prostate had significant reduction in prostatic acid-phosphatase levels. The greatest depression in phosphatase concentration occurred in patients sensitive to antiandrogen therapy, indicating that the test may detect carcinomas resistant to hormone therapy and may also determine the androgenic activity of the various synthetic estrogens.

Muhsen, J.: Possible significance of the prostatic secretion acid phosphatase as a diagnostic and a prognostic index in carcinoma of the prostate. J. Urol. 72:928-933, Nov., 1954.

A Century and a Quarter Ago

If there be a principle of universal application and acceptance in modern surgery, it is that which enforces the earliest possible removal of a true scirrhus. Whence is this derived but from repeated failures, attributed, and justly, to procrastination?

Travers, B.: Observations on the Local Diseases Termed Malignant. London, G. Woodfall, 1829.

a glance . . .

one-minute abstracts of the current literature on cancer . . .

Chemotherapy of Human Cancer

Because of the limitations of surgery and radiation therapy in effecting a cure for cancer, chemotherapy is being explored with the hope of finding some agent that will cure neoplasms without harming the normal systems, functions, or cells within the body. Although a number of chemotherapeutic agents are of value in the inhibition of animal tumors, they may not be of value in man. Hence the ultimate test of these agents lies in the evaluation of their effects in human cancer. The chemotherapeutic agents that are presently of value include the folic acid antagonists, the purine antagonists, the nitrogen mustards, the ethyleneimines, myleran (GT-41), urethane, Fowler's solution, and hormones.

Studies on the mechanism of action of the folic acid antagonists indicate that these substances interfere with nucleic acid synthesis. Before the folic acid–antagonist era, children with acute leukemia rarely lived for one year after the diagnosis was established, and the spontaneous remission rate varied from 1 to 10 per cent in these cases. Reports from numerous investigators at a conference held in 1951 showed that the average remission rate in children with acute leukemia was about 50 per cent in those treated for one day or longer with anti–folic acid compounds. Farber's compilation of seven separate investigations of the results of treatment of acute leukemia with the compounds in 425 children and fifty-two adults treated fourteen days or more showed 68.5 per cent improvement among the children and 13.5 per cent among the adults. The most widely used folic acid compounds are aminopterin and amethopterin.

Wright, J. C.: Chemotherapy of human cancer. Tr. New York Acad. Sc. 17: 210-236, Jan., 1955.

Are Hormones Carcinogens?

Certain sex hormones induce malignant change in animals susceptible to cancer, giving rise to the impression that similar change in man might be induced by, for example, long-continued massive doses of estrogen. Other experiments show that tumorigenesis, occurring at the site of implantation in the spleen of small pieces of ovarian tissue in castrated animals, may be prevented by the administration of estrogens. Breast cancer has been reported

in men following intensive estrogen therapy for prostatic cancer. Endometrial cancer is increased in incidence in the presence of granulosa- or theca-cell tumors. Thus, it is seen that prolonged increased estrogen levels, of intrinsic or extrinsic origin, may be inciters of cancer when the genetic factors are present. Estrogens are useful in the palliative treatment of cancer of the breast in postmenopausal women. The few cases of mammary or uterine carcinoma following hormone therapy should be considered incidental. Until there is more convincing evidence that hormones are tumorigenic for man, they should not be withheld in those cases in which their advantages far outweigh the remote possibility of their being carcinogenic.

Greenblatt, R. B.: Hormones, carcinogenesis, and geriatrics. [Editorial.] Geriatrics 10: 46-47, Jan., 1955.

Intracavitary Radiocobalt for Bladder Tumors

Intracavitary irradiation with radiocobalt frequently destroys urinary-bladder lesions that are not deeply infiltrating. The treatment technique consists of placing a radiocobalt bead in the central channel of a balloon catheter so that the bead is held at the geometric center of the bladder when the bag is inflated. The catheter has special perforations that permit the outflow of urine. When the lesion has spread beyond the walls of the bladder, radiation is employed only to stop some of the distressing symptoms, such as bleeding, inflammation, edema, and pain. A palliative beneficial effect may be achieved with doses varying between 300 and 1500 r over a period of one to three weeks. Intracavitary irradiation with radiocobalt alone or in combination with local roentgen-ray treatment was used in thirty-five patients with urinary-bladder tumors in various stages of invasion. Radiation cystitis and bladder contraction frequently result from therapy. When tumor eradication or arrest is the goal of treatment, untoward effects of radiation must be anticipated as unavoidable sequelae of any intensive radiation. If palliation is the aim, the dose should be limited to avoid untoward effects. With palliative treatment, bleeding and pain may be checked for weeks or even months. Treatment may be repeated at intervals as necessary.

Hinman, F., Jr.; Schulte, J. W., and Low-Beer, B. V. A.: Further experience with intracavitary radiocobalt for bladder tumors. J. Urol. 73: 285-291, Feb., 1955.

Chemotherapy of Leukemia

Several chemotherapeutic agents—nitrogen mustard, triethylenemelamine, myleran, colcemide, aminopterin, amethopterin, ACTH, cortisone, 6-mercaptopurine—are available for application to Hodgkin's disease and the leukemias. Satisfactory remissions and palliation, but not cure, can be obtained by their use. The family physician may be called upon to use these products in patients unable to travel to radiological centers because of illness or because of the expense involved. He should, therefore, acquaint himself with the use of these agents and should guard particularly against overtreatment. Preference is given to nitrogen mustard in Hodgkin's disease; to triethylenemelamine in chronic lymphocytic leukemia; to urethane, myleran, and colcemide in chronic myelocytic leukemia; and to the folic acid antagonists, aminopterin and amethopterin, and ACTH, cortisone, and 6-mercaptopurine in acute leukemia.

Bernard, J. A.: Chemotherapy of leukemia and related disorders. Southwestern Med. 36: 12-13, Jan., 1955.

Radioactive Iodine in Malignant Melanoma

In order to determine the usefulness of I^{131} as a therapeutic agent in malignant melanoma, the authors performed I^{131}-tracer studies on eight of nine patients with proved malignant melanoma, all of whom had regional or distant metastases. External survey counts, direct counts of biopsy specimens, and radioautographs of biopsy specimens were obtained at intervals following the administration of 1- to 5-mc. tracer doses. In no case was there

any evidence of selective uptake of I^{131} by the tumor tissue. In spite of this, therapeutic trial doses of 50 to 65 mc. of I^{131} were given. An attempt was made to block iodine uptake by the thyroid gland with thyroid extract. None of the patients showed subjective or objective improvement nor was there any evidence of prolongation of life.

Kory, R. C.; Tucker, R. G., and Meneely, G. R.: Radioactive iodine in malignant melanoma. Am. J. Roentgenol. 72: 119-123, July, 1954.

Nitrogen Mustard in Lung Cancer

Previous reports indicate that from 18 to 74 per cent of patients with bronchogenic carcinoma treated with nitrogen mustard were benefited. Best results are obtained when this therapy is limited to the small-cell type of bronchogenic carcinoma. Nine of ten patients with this type showed significant subjective or objective improvement. Four showed significant regression of lung involvement by roentgenogram. Among twenty-two patients with other cell types of bronchogenic carcinoma—squamous-cell, adeno-, alveolar-cell, and undifferentiated (anaplastic)—only three showed slight subjective improvement, and one of undetermined type showed improvement in neurological signs from brain metastases. The total dose in one course was from 0.4 to 1.5 mg. per Kg. of body weight intravenously, either in a single dose or in divided doses on successive days. In treatment of bronchogenic carcinoma with nitrogen mustard, only patients with small-cell type can be expected to benefit significantly.

Levine, B., and Weisberger, A. S.: The response of various types of bronchogenic carcinoma to nitrogen mustard. Ann. Int. Med. 42: 1089-1096, May, 1955.

Chemotherapy of Leukemias and Lymphomas

Good remissions and significant prolongation of life in a high percentage of children with acute leukemia may now be obtained by use of the newer chemotherapeutic agents—antifolic drugs; nucleic acid inhibitors; and the corticosteroids, alone, in sequence, and in combination. These agents have not supplanted the former methods of management—radiation, blood transfusions, and antibiotics—and there is no evidence, except in the acute leukemias of childhood, that life has been prolonged. No cure for these diseases is yet in sight. Among the nucleic acid antagonists, 6-mercaptopurine gives good remissions in about 60 per cent of acute leukemias and in some instances of chronic granulocytic leukemia. Therapeutic use of this compound is based on its antagonism to adenine and hypoxanthine in the metabolism of desoxyribosenucleic acid. Among the cytotoxic agents are colchicine, urethane, the nitrogen mustards, myleran, ACTH and cortisone, triethylenemelamine, and triethylenephosphoramide. Among the antimetabolites are the folic acid antagonists: aminopterin, amethopterin, and aminoanfol, and the nucleic acid inhibitor, 6-mercaptopurine.

Leonard, M. E.: Chemotherapy of the leukemias and lymphomas. Am. Pract. & Digest Treat. 6: 95-98, Jan., 1955.

Corticosteroid plus HN2 in Cancer

The treatment of the incurable-cancer patient is a formidable problem. Any regimen yielding to the patient a fair degree of comfort with minimal use of narcotics is desirable. A combination of ACTH or cortisone with nitrogen mustard was tried by the author first in resistant and advanced cases of lymphosarcoma and Hodgkin's disease with gratifying palliation, without severe nausea, vomiting, or bone-marrow depression, and with unusual remissions for intervals of as long as three years. This combined therapy was extended to include advanced or terminal cancers of breast, lung, stomach, pancreas, colon, uterus, bladder, prostate, etc.—a total of 100 cases, with excellent results in sixteen, good results in fifteen, and fair results in twenty-nine. All treatments were given in the hospital under close supervision. ACTH (60 to 80 units) or cortisone (50 to 75 mg.) was given twelve to eighteen hours before the first of five daily intravenous injections of

nitrogen mustard, 0.1 mg. per Kg. of body weight. ACTH was administered intramuscularly every six hours, the dose being gradually diminished on the last of the five or six days of hospitalization. Cortisone was more effective than ACTH in cancer of the breast and prostate and was given orally or parenterally every four hours to a total dose of 300 to 450 mg. daily. After the patient left the hospital, a daily dose of 100 to 200 mg. cortisone, with 3 to 4 gm. potassium chloride and small doses of testosterone, was given. Patients responding to this initial course of therapy were given similar second and third courses at monthly intervals. The severe nausea, vomiting, and leukopenia invariably produced by nitrogen mustard were absent or markedly reduced in this combined therapy. Decreased narcotic consumption, good palliation, and prolongation of life resulted from this additive or synergistic therapeutic regimen.

McCarthy, W. D.: The palliation and remission of cancer with combined corticosteroid and nitrogen mustard therapy: a report of 100 cases. New England J. Med. 252: 467-476, March 24, 1955.

Thio-TEPA in Leukemia

Nine cases of chronic granulocytic leukemia and two cases of chronic lymphocytic leukemia were treated intravenously, intramuscularly, and orally with thio-TEPA for periods up to twenty months. Clinical or hematological remissions were induced in all cases. The only untoward side effect was temporary bone-marrow depression. In this respect this drug is superior to nitrogen mustard and triethylenemelamine. Thio-TEPA exerts a profound effect on the leukocyte count and gives improvement in the hemoglobin value. Clinical improvement is shown by gain in strength and weight and by a remarkable reduction in the size of the spleen and of the enlarged lymph nodes. Thio-TEPA is concluded to be of value in the management of co-operative patients with chronic leukemia.

Zarafonetis, C. J. D.; Shay, H., and Sun, D. C. H.: Triethylenethiophosphoramide in the treatment of chronic leukemia. Cancer 8: 512-522, May-June, 1955.

Differences in Radiomimetics

Ionizing radiations, nitrogen mustard, and triethylenemelamine (TEM) apparently have different mechanisms of action, even though the agents have similar biological effects. Lethal doses of roentgen-ray radiation or nitrogen mustard may be counteracted in mice by previous administration of cysteine, β-mercaptoethylamine, or sodium nitrite. However, administration of the protective compounds to animals given lethal doses of TEM does not alter the toxic effects of the drug.

Nadkarni, M. V.; Goldenthal, E. I., and Smith, P. K.: Observations on the comparative protective action of certain compounds against the lethal effects of triethylene melamine, nitrogen mustard, and x-radiation. [Abstr.] Proc. Am. A. Cancer Research 1 (2): 34, 1954.

Cancer Chemotherapy

Though several chemotherapeutic agents are effective against lymphomas, palliative therapy of epithelial tumors is more difficult. Rate of growth of epitheliomas is slow, so a drug probably must be administered over a long period of time and must be well tolerated by the host cells. The phosphoramides seem to be the most effective treatment for adenocarcinoma of the breast and ovary and for tumors of the central nervous system. Results are most pronounced when the agents are given locally, especially intrapleurally or into abdominal masses. The drugs may also be injected into vein, muscle, artery, peritoneal cavity, pericardium, or cranium. Thio-TEPA was administered to thirty-four patients with far-advanced mammary carcinoma not suitable for surgery or irradiation. Previous therapy included operation, radiation, and hormones. Subjective improvement was reported by twenty-five patients, and thirty-one individuals showed signs of improvement lasting four to eleven months. Among twenty-one persons beneficial effects are currently increasing. Objective signs of improvement include regression of soft-tissue lesions, partial to complete healing of ulcerations, control of pleural effusion, reduction in ascites, roentgen-ray

evidence of healing of bone lesions, and control of signs and symptoms of brain metastases. Pain, pruritus secondary to extensive inflammatory carcinoma, dyspnea, cough, and dysphagia are often decreased and the sense of well-being and the appetite may increase. Of the total group of ninety-six patients with cancer at various sites who received thio-TEPA, approximately 83 per cent improved.

Bateman, J. C.: Cancer chemotherapy, M. Ann. District of Columbia 24: 55-62, Feb., 1955.

Protection against Aminopterin Toxicity

Multiple injections of aminopterin, with citrovorum factor given twelve hours after each injection, appear to produce the greatest amount of tumor damage with the least toxicity in mice inoculated with leukemia. Since the tumor has a lower reserve of endogenous protection against aminopterin toxicity than has the host, the delay in administration of citrovorum factor permits aminopterin to damage the leukemic tissue irreversibly while the host's endogenous reserve of protection still maintains it. The delayed citrovorum factor then protects the host but cannot reverse the damage to the tumor. When citrovorum factor is given too soon after aminopterin has been administered, the tumor is protected as well as the host; if given too late, irreversible damage may be done to the host as well as the tumor.

Goldin, A.; Venditti, J. M.; Humphreys, S. R.; Dennis, D.; Mantel, N., and Greenhouse, S. W.: Factors influencing the specificity of action of an antileukemic agent (aminopterin). Multiple treatment schedules plus delayed administration of citrovorum factor. Cancer Research 15: 57-61, Jan., 1955.

Thio-TEPA in Inoperable Cancer

Triethylenethiophosphoramide (thio-TEPA), a congener of nitrogen mustard used successfully in the treatment of chronic leukemia, gave the authors encouraging results in two patients with recurrent metastatic cancer of the breast. This led them to apply the carcinolytic properties of this compound to forty-seven patients with cancers no longer suitable for surgery or responsive to irradiation or other therapy. This group included cancers of the breast, ovary, lung, larynx, esophagus, stomach, small and large intestine, thyroid, biliary tract, and prostate. Thio-TEPA can be administered intramuscularly, intravenously, and locally into the tumor. Patients with carcinoma of the breast and of the ovary showed objective evidence of improvement, with survivals as long as twenty-one months. Patients with cancers of other sites were benefited little, if any. Indications for the drug are similar to those well established for nitrogen mustard. During administration of the drug white-cell counts should be made daily and complete blood-cell counts, including platelets, weekly. Frequent bone-marrow studies should be done, and, if the aspirate is hypocellular, the drug should be discontinued until the cell count returns to normal.

Shay, H., and Sun, D. C. H.: Clinical studies of triethylenethiophosphoramide in the treatment of inoperable cancer. Cancer 8: 498-511, May-June, 1955.

Adrenalectomy in Prostatic Cancer

Bilateral adrenalectomy was performed on six patients with advanced carcinoma of the prostate, with no operative mortality. One died five, one died eight, and one died fourteen months after operation. One is living two and one-half, and one five and one-half, months after operation. The sixth patient, last seen five months after operation, showed increase in size of his prostate and increased pain from skeletal metastases. The other five were relieved of pain almost immediately after adrenalectomy for from a few weeks to fourteen months. There was definite evidence of regression in four cases as determined by reduction in prostatic size and in one case by a reduction in the size of the abdominal lymph nodes. Elimination of adrenocortical function after a period of remission induced by castration and estrogen therapy results in a second period of remission for some and marked relief from pain in most patients. However, the results do not justify any great enthusiasm, and the procedure should be considered

only as a last-ditch fight in a gradually losing battle for each individual patient. Hope is expressed for the eventual development of a hormone, a congener of cortisone, that will depress adrenocortical function, achieving nonsurgical adrenalectomy.

Ray, E. H.: Bilateral adrenalectomy in carcinoma of the prostate. J. Urol. 73: 712-715, April, 1955.

Radiogold Therapy of Bladder Tumors

Neoplasms originating in the bladder may be destroyed or inhibited by direct injections of radioactive colloidal gold. When the tumor is large, the bladder is opened suprapubically, the major portion of the growth removed, and the base injected with 1 cc. of solution for each cubic centimeter of neoplastic tissue remaining. Small tumors may be excised and injected through the cystoscope. The injections produce definite degenerative changes in malignant tissue without affecting healthy mucosa or causing toxic reactions. The technique seems as effective as radium, radon seed, or roentgen-ray therapy.

Nelson, C. M.: Use of radioactive gold in the treatment of carcinoma of the bladder: report of 8 cases. South. M. J. 48: 245-250, March, 1955.

Myleran in Leukemia

Over a period of four years thirty-one patients with chronic myeloid leukemia were given repeated courses and maintenance therapy with myleran. It relieved symptoms, reduced the size of spleen and liver, and improved the blood picture, especially the hemoglobin, comparing favorably with radiotherapy, particularly for its ease of administration. Myleran is ineffective in acute leukemia and in chronic myeloid leukemia in myeloblastic relapse. When doses exceeding 0.08 mg. per Kg. of body weight were avoided, there were no side effects, including thrombocytopenia. Remissions after second and third courses were shorter than those from the first course of therapy. The short intensive course of 100 to 150 mg. in one to six days was abandoned in favor of a standard daily adult dose of 4 mg. Maintenance doses varied from 0.5 to 8 mg. daily. Specific resistance to myleran developed in three patients. Re-treatment was deferred until symptoms returned. Patients on maintenance therapy remained well for periods up to two years. Myleran is a satisfactory substitute for radiotherapy. Its chief advantage is its efficacy when radiotherapy has been of limited value or has lost its efficacy.

Galton, D. A. G., and Till, M.: Myleran in chronic myeloid leukaemia. Lancet 1: 425-430, Feb. 26, 1955.

Adrenalectomy for Breast Cancer

Fifty-six bilateral adrenalectomies in advanced and disseminated breast cancer are reported. About one third of the patients were no longer under hormonal influence and accordingly obtained no benefit. Improvement in the remaining two thirds varied from complete control of the disease to amelioration varying in degree and duration. The longest period of improvement was twenty-four months. Only patients to whom nothing further could be offered were included in this group. All had widespread skeletal, visceral, or soft-tissue metastases, and life expectancy was very limited. Operative risk was high in patients with disseminated disease in the pulmonary lymphatics, with involvement of the pericardium and heart. Impaired lung and heart function is the main contraindication. There is no method of predicting which patients will be benefited by the operation. When improvement occurs —in about 60 per cent of patients—it is quite remarkable and surprising. Among the benefits are relief of pain from skeletal metastases, regression of palpable lesions, reossification, and union of pathological fractures—subjective and objective improvement never previously accomplished by any other method of treatment.

Cade, S.: Adrenalectomy for breast cancer. Brit. M. J. 1: 1-5, Jan. 1, 1955.

Cancer Chemotherapy and the Structure of DNA

L. D. Hamilton, D.M.

Our increasing knowledge of nucleic acids has been a major factor in dissipating the pessimism that has long shrouded the search for cancer-controlling chemicals. Indeed, a leading scientist in the nucleic acid field has recently entitled a paper *Metabolic Basis for Optimism Regarding Chemotherapy [Cancer] with Nucleic Acid Derivatives*. The nucleic acids have thus not only removed a long-standing psychological barrier but also have provided an important practical basis for cancer chemotherapy.

Empiricism and Antimetabolites

The natural sciences are essentially empirical and the science that underlies cancer chemotherapy is no exception. Thus aminopterin and amethopterin, antagonists of folic acids, were found to be useful palliative agents in the treatment of acute leukemia in children before any knowledge of the intimate mechanism of their chemotherapeutic effect had been achieved. These agents were considered to be simply antimetabolites of folic acids—a conclusion derived from their pharmacological effects in animals, which closely resembled those produced by folic acid deficiency. But because the role of folic acids in cell metabolism awaited definition, this conclusion was unsatisfying. It is only in the last few years that evidence has accumulated that the folic acid antagonists prevent cells from using single carbon atoms for the synthesis of several amino acids (building blocks for protein) and also prevent the use of these carbon atoms for the building of purines and pyrimidines, essential constituents of nucleic acids.

From the Sloan-Kettering Institute for Cancer Research, Memorial Center for Cancer and Allied Diseases, New York, New York.

Azaserine, an antibiotic substance isolated from a micro-organism, *Streptomyces*, is another kind of chemical picked up in an empirical screening program. Azaserine is a most effective chemotherapeutic agent in the treatment of a transplantable mouse tumor (sarcoma 180); it is doubtful whether azaserine alone will be useful against human cancer. Its formula might suggest that azaserine was acting as an antimetabolite against the important amino acid serine, but very recent work has shown that this compound instead prevents closure of the purine ring and thus inhibits nucleic acid synthesis. This blockage of nucleic acid synthesis led to the accumulation of hitherto undetected intermediate compounds in the construction of nucleic acids in cells. In the first publication on azaserine it was predicted that the compound would be a good tool for biochemical studies: this new knowledge of nucleic acid synthesis bears out this prediction.

The folic acid antagonists and azaserine are, then, two very different kinds of chemicals that were found to inhibit some cancers and that were subsequently shown to act mainly by interfering with nucleic acid synthesis.

6-Mercaptopurine (6-MP) represents still another type of anti-cancer compound in clinical use for the palliation of cancer. It imitates the structure of the purine constituents of nucleic acids. It is very much like the natural purine, adenine. The discovery of the tumor-inhibiting action of 6-MP is sometimes referred to as an example of enlightened empiricism. This term was used (1) because 6-MP, an analogue of adenine, was successful as an oncolytic agent and (2) because, in the chemotherapy screening program at the Sloan-Kettering Institute, some 6 per cent of 1000

purines, pyrimidines, and related compounds had some anti-tumor activity, while the corresponding figure for more than ten thousand other compounds of many types tested was 3 per cent.

It has been suggested that one way in which 6-MP inhibits growth is by getting itself incorporated into nucleic acids, presumably by slipping into the position left open for the natural purine adenine; indeed such a mechanism has been postulated for several purine and pyrimidine analogues and actual incorporation into nucleic acids has been demonstrated for some of these analogues. The purine adenine is found not only in nucleic acids, but also in cofactors for extremely important enzymes. It is conceivable therefore that part of the action of 6-MP might result from its replacing adenine in these coenzymes. Recently some evidence has appeared that 6-MP might also prevent the completion of the purine ring at a different step from that blocked by azaserine. Again the growth-inhibiting effect of 6-MP depends on its interfering with the building of nucleic acids.

DNA and Cell Growth

Why are chemicals that interfere with nucleic acids prone to inhibit the growth of cancer? All the available evidence from classical cytology and genetics indicates that the chromosomes contain the controlling equipment, the genes, that determine the character and rate of growth of cells. Chromosomes contain protein, deoxyribosenucleic acid (DNA), and a little pentosenucleic acid (PNA). The weight of evidence is that DNA alone is the key, even likely the actual substance, of the gene, responsible for the specificity of the hereditary material. The hereditary character of bacteria can be permanently changed by treatment with DNA alone extracted from another strain of the same species; e.g., pure DNA obtained from streptomycin-resistant pneumococci, when incubated with streptomycin-sensitive pneumococci, will confer resistance to streptomycin not only on organisms that were exposed to the DNA but also on their offspring. This process achieved with DNA is known as bacterial transformation, of which there are now many examples. The infection of bacteria by tiny viruses (bacteriophages), which ultimately lyse the bacteria, affords additional strong evidence that DNA is the hereditary material. It is the DNA of the phage that penetrates the bacterial cell leaving the protein of the phage outside, and it is this DNA that appears capable of self-replication in the bacterial cell, with the production of numerous new phages.

Some English scientists like to envisage mitosis, when the cell divides and becomes two, leaving behind two sets of chromosomes where only one existed before, as "the microscopical ballet of reproduction," with DNA the ballet-master. In American parlance, we regard DNA as the top executive of the cell. Both conceptions assume DNA to be the fabric of the gene; thus chemicals that interfere with the synthesis of DNA will prevent cell division and hence might inhibit cancer growth.

DNA Structure and DNA Specificity

Although it is now clear why chemicals that prevent DNA replication prevent cell growth, the question of why cancer cells may be more vulnerable than normal cells remains unresolved. This question of specificity assumes particular pertinence because the work leading to the three-dimensional structure of DNA, while emphasizing the basic similarities of DNA's, also provides a model for an infinite number of differences among DNA's. Wilkins and his associates in London found that X-ray diffraction of fibers of DNA extracted from cells gave pictures indicating that the molecules of DNA were aligned regularly in three dimensions. They further found that there was no difference in the crystalline patterns of DNA's prepared by R. K. Barclay and me at the Sloan-Kettering Institute in New York; these DNA's were extracted from a wide variety of species such as calf thymus, mouse, and man, includ-

ing normal and leukemic leukocytes and other sources. It was this evidence of geometric regularity in the giant molecule of DNA in all species that, with the specific-pairing hypothesis of Watson and Crick, allowed construction of a three-dimensional model for DNA. It should be stressed that the three-dimensional structure of the molecule required first that the chemical formulas of the various building blocks of DNA should be already fully established by chemists.

This x-ray work, taken together with the derived, very long, filamentous double-helix molecules that are now known to exist in living cells, implies that the basic structure, the skeleton, of DNA is the same in all cells. This generalization would apply to both cancer and normal cells.

Wherein resides the specificity of DNA? The most obvious chemical differences among DNA's from different species are variations in the amounts of the nitrogenous building blocks, the purines and pyrimidines. In DNA from nearly fifty species the amounts of adenine and thymine are about equal and the amounts of guanine and cytosine are about equal too. In contrast, the ratios of adenine to guanine and of thymine to cytosine vary considerably in different species. These analytical data give strong support to the Watson and Crick specific-pairing hypothesis that in the DNA structure adenine is always cross-matched with thymine and guanine with cytosine. The analytical data also give a clue that the specificity of DNA may be determined by these nitrogenous building blocks; but much more importantly the three-dimensional structure suggests that the arrangement of these building blocks in the DNA molecule is the basis for the specificities of DNA and for their specific copying in genetic processes. The linear sequence of the purine-pyrimidine pairs along the helical coils is not known but their potential variability in structure suggests that specificity is determined by these sequences. In this way the sequences would act as a genetic code spelling out different hereditary attributes. These sequences would be responsible, for example, for the unequivocal specificity of the DNA bacteria-transforming factors; and recently there have been reports of the separation by chromatography of DNA obtained from streptomycin-resistant pneumococci into a number of fractions differing both in chemical composition (nitrogenous-base ratios) and in transforming ability. These developments open the possibility of establishing the chemical composition of a single gene. Since all evidence indicates that cancer cells result from modifications of the genetic equipment of normal cells, this implies that it may be possible to pinpoint the specific chemical differences in the DNA of cancer cells.

DNA Specificity and Chemotherapy

The determination of what building blocks are used by different species and

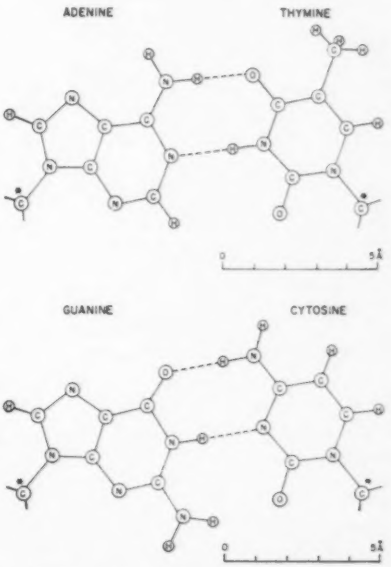
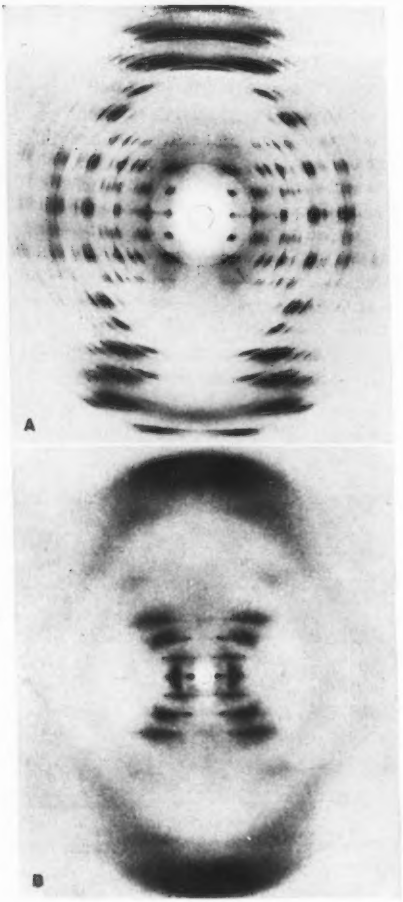
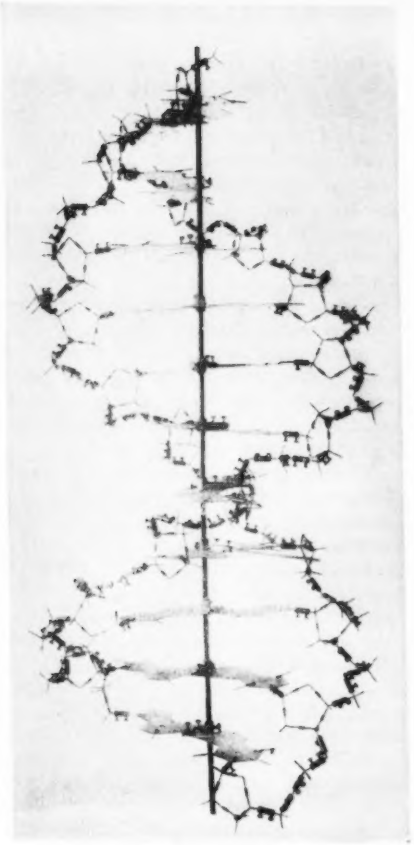


FIGURE 1. Special pairing of nitrogenous bases proposed by Watson and Crick. Hydrogen bonds are shown dotted. ©* represents carbon 1 of the deoxyribose of each helical sugar-phosphate chain. Above: Pairing of adenine and thymine. Below: Pairing of guanine and cytosine.

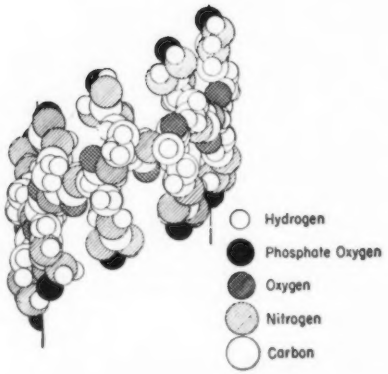


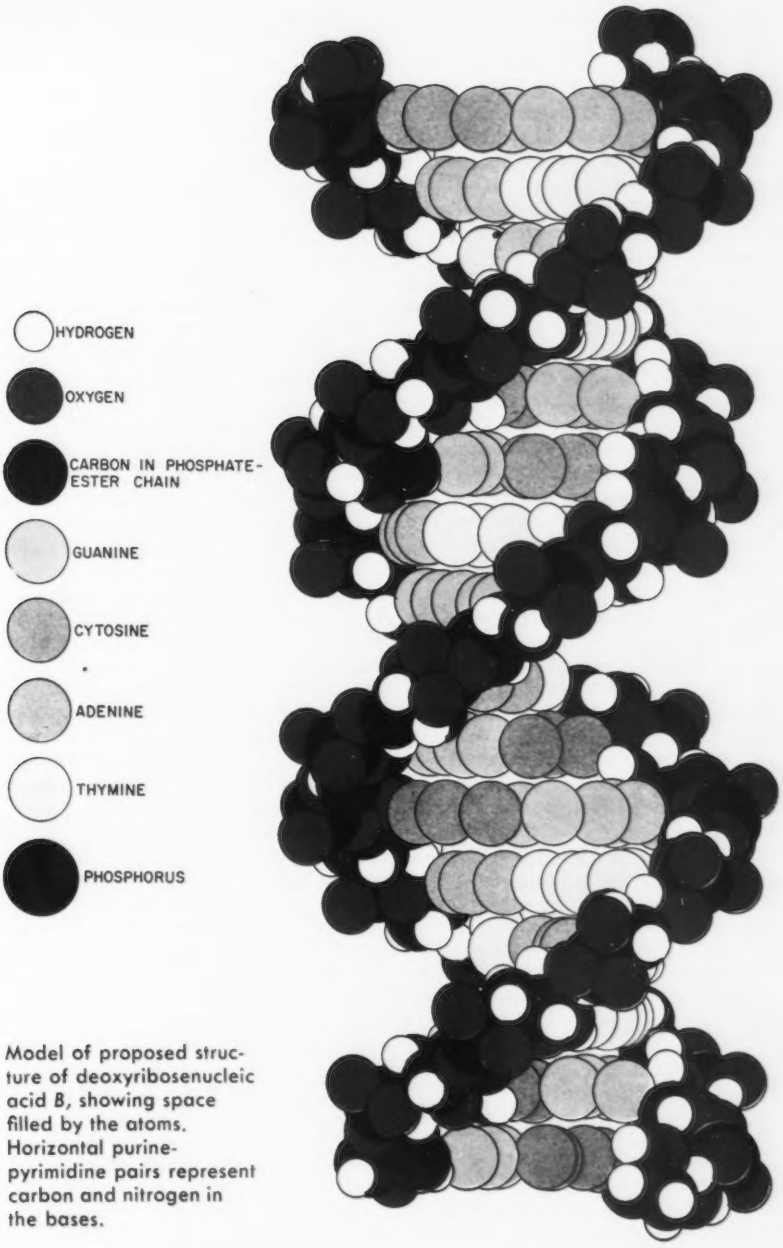


Above: X-ray fiber diagrams of deoxyribosenucleic acid. A, crystalline A structure. B, Crystalline B structure.

Upper right: Working model of proposed structure of deoxyribosenucleic acid B.

Lower right: Model of proposed structure of nucleopoly-L-arginine, i.e., a special nucleoprotein.





Model of proposed structure of deoxyribosenucleic acid *B*, showing space filled by the atoms. Horizontal purine-pyrimidine pairs represent carbon and nitrogen in the bases.

different cells for nucleic acid synthesis has revealed that there are qualitative or large quantitative differences in anabolic patterns; for example, there is a considerable diversity in patterns of purine utilization for nucleic acid synthesis. It is upon differences of this sort that the use for cancer chemotherapy of analogues of these building blocks is predicated—it is hoped that they might interfere with these anabolic processes. For this purpose it does not matter if the predominant pathway for nucleic acid synthesis is from single atoms rather than from preformed building blocks. Similarly it would not matter if, as is probable, the actual steps to nucleic acid synthesis are the same in the cancer cell and the normal cell. As long as the antimetabolite can slip into the pathway for nucleic acid synthesis and providing, as the evidence suggests, there are differences in the accessibility and capacity of the metabolic pathways, the antimetabolite could still selectively inhibit the cancer cell.

Just as the chemical formulation of the building blocks of DNA has permitted the design of antagonists for these building blocks, so it is reasonable to expect that this new knowledge of the arrangement in space of the building blocks of DNA and the impressive possibilities for determining the site of DNA specificity will provide a new target for "rational cancer chemotherapy."

DNA—the Chemical Agent?

Biochemists over the last two decades have emphasized the "dynamic equilibrium" of cellular constituents. By this they mean the continuous building up and breaking down of molecules. In contrast DNA molecules are relatively stable, and it appears that new DNA is produced only for new cells. It would seem unlikely that DNA of the parent cells, if it is to serve as a pattern for inheritance for its offspring, would break down before or during cell division but rather that it would be passed on with new DNA to new cells.

The transforming activity of bacterial DNA suggests that bacteria can incorporate relatively large portions of the DNA macromolecule into their own pre-existing DNA. This incorporation doubtless takes place only at the time when bacterial DNA is replicating, before the growth of new bacteria. Subsequently, the incorporated transforming DNA serves as an additional template for inheritance, and hence the offspring of the transformed bacteria reproduce with their new hereditary characteristic.

There are some hints in the literature that such reutilization of large fragments of DNA also occurs in mammals, and I have recently obtained data in man, one interpretation of which is that such reutilization takes place in human leukemic lymphocytes. If this suggestion of reutilization of large chunks of DNA can be substantiated, it would be a further encouragement to design antimetabolites molecularly larger than those hitherto used that, in turn, may displace specific portions of the DNA macromolecule. Such antimetabolites would be better able to exploit specific differences between normal and cancer cells.

Credits

The illustrations on pages 162 and 163 were provided by Dr. W. E. Seeds and Dr. H. R. Wilson, Wheatstone Physics Laboratory, King's College, London (their work has been aided by research grants from the British Empire Cancer Campaign) and by Dr. L. D. Hamilton, Sloan-Kettering Institute, New York (work aided by grant from the National Cancer Institute, of the National Institutes of Health, Public Health Service, and Scholar grant from the American Cancer Society).

Chemotherapy of Cancer

David A. Karnofsky, M.D.

Once cancer spreads beyond the site of origin, or when it appears initially as a disseminated disease, its subsequent and inexorable progression is determined largely by the biological characteristics of the disease in relation to the environmental situation provided by the host. The physician, in the past, has been frequently an interested but ineffectual observer, and this frustrating role has led to therapeutic discouragement and apathy. Roentgen-ray therapy has been an invaluable palliative tool, but after fifty years its ultimate limitations are apparent; furthermore, adequate radiotherapy is not easily available to all physicians. Only in recent years, beginning in the late 1930's, were systematic efforts made to control the growth of certain forms of cancer by altering its physiological environment, and later, in the middle 1940's, were drugs developed that temporarily restrained the growth of certain forms of neoplastic disease. Thus, in this brief period a new phase of cancer therapy was established—the search for drugs that could control, restrain, or destroy the growth of neoplastic cells wherever they existed in the body. A great deal of deliberate optimism was necessary to stimulate the growth of this field against the negativism that pervades any efforts to treat far-advanced or nonresectable cancer. Now a sound basic discipline of cancer chemotherapy is evolving.

History

Harbingers of effective chemotherapeutic agents for neoplastic disease were Fowler's solution, first reported by Lissauer for the treatment of leukemia in 1865; Coley's bacterial toxins, which Coley, beginning in 1893, valiantly strove to prove of therapeutic value; and benzene, applied in 1912 by Koranyi for the treatment of leukemia. The modern era began in 1941 when Huggins demonstrated that orchiectomy would temporarily control the growth of prostatic cancer; similar therapeutic results were also obtained with estrogenic hormones. During the same period it was also shown that breast cancer could be temporarily inhibited, and sometimes stimulated, by the use of exogenous sex hormones. Not until 1950 was the therapeutic activity of the adrenal steroids utilized in human cancer.

Another major development began in 1938, when radioactive isotopes became available for clinical use. While these agents act by means of their radioactivity, their chemical properties determine their metabolic fate and tissue localization. This form of treatment was introduced in the early reports on radioactive phosphorus in disorders of the blood-forming organs and on radioactive iodine in the treatment of thyroid disease.

During World War II, nitrogen mustard, a potential war gas, was found by Goodman, Gilman, and Dougherty and by Jacobson to be of therapeutic value in the lymphomas, and extensive clinical trials were begun in 1945. Nitrogen mustard and its related compounds were a great stimulus to cancer chemotherapy; they were not physiological agents or radioactive substances and they exhibited a regular, measurable, and reproducible therapeutic effect in the lymphomas, chronic leukemias, and lung cancer.

In 1948 Farber found that the 4-amino analogues of folic acid would produce remissions in acute leukemia in children. By this demonstration of antimetabolite activity in cancer, an important theoretical approach to cancer chemotherapy was put on a practical basis. The continuing search

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for other antimetabolites selectively injurious to cancer cells has led to the recent clinical observation by Burchenal that 6-mercaptopurine is also effective in acute leukemia.

These few compounds are the distillate from clinical studies on hundreds of drugs. They are the first limited steps but they are a beginning toward the goal of developing chemicals for the control of cancer.

Search for Effective Agents

It is apparent that a brilliant, novel concept can at any time change the approach to cancer chemotherapy. At present, the search for effective agents is proceeding on several distinct levels.

Screening. Empiricism is a major approach to chemotherapy, whereby many chemicals and biological substances are screened for tumor-inhibiting activity in laboratory animals. Empiricism is sustained by the fact that many diseases have been successfully treated before their cause or pathogenesis or the mechanism of action of the therapeutic agents was established. Moreover, the discovery of an effective treatment may lead to an understanding of the disease. When the screening method discloses chemicals with cancer-inhibiting activity, these discoveries have far-reaching fundamental as well as therapeutic implications.

Thousands on thousands of chemicals, tissue extracts, and filtrates of bacteria and fungi are being tested for tumor-inhibiting activity. The test systems used are of critical importance, since they determine whether a drug is discarded as negative or merits further study. In most procedures, mice or rats inoculated with a transplantable tumor are given the maximum tolerated dose of the test compound; the ability of the drug to inhibit tumor growth is the measure of therapeutic activity. Since different tumors do not respond uniformly to active agents, several types of transplantable tumors are used, such as mammary carcinoma, osteogenic sarcoma, lymphosarcoma, melanoma, and leukemia. In some instances spontaneous mouse tumors are used. Recently, human carcinomas and sarcomas have been grown by continuous passage in cortisone-treated rats and hamsters and in chick embryos; these are being adapted for screening procedures. The availability of these transplantable human tumors may make it possible to test candidate drugs directly against human-cancer cells. Secondary screening methods are concerned with the effects of drugs on the growth of embryonic tissue, of bacteria, of fungi, and of viruses.

In 1954 the American Cancer Society sponsored a co-operative project under the direction of Gellhorn to assess the validity of screening methods; this survey settled no problems. Twenty-seven standard drugs were tested in seventy-four different potential screening systems. Different tumors and the various nontumor screening systems responded diversely to the same drugs. These results emphasize that the tumors, because of differences in chemical composition or metabolism, and the varied nontumor screening discern different pharmacological activities of a test drug. Thus, in principle, a potential chemotherapeutic agent that is active in only one particular system or against one particular type of tumor could be missed in a restricted laboratory and clinical screening program. Yet it is not feasible to test all drugs by all methods. It is also possible that a truly curative agent would be active in all these screening systems, the apparent weaknesses and inconsistencies in our screens being due to the fact that they are not being presented with highly specific oncolytic agents. There is no simple solution to the screening dilemma. The difficulties will continue until a system can be defined that bears a direct and consistent relationship to a metabolic peculiarity or etiological agent associated with a specific type of human cancer or is present in all forms of cancer. Screening systems are being improved whenever possible, in part by correlating the activity of a drug in each screening system with its therapeutic activity in man.

Current Research. The complex of can-

cer research resulting from its many supporting disciplines provides a large reservoir of information and leads for chemotherapeutic investigations. Studies on the fundamental characteristics of the cancer cell and how it differs from normal cells are of enormous importance to cancer chemotherapy. These investigations are concerned not only with the characteristics of cancer in general, but also with the special features of the many different types of neoplastic disease. Furthermore, since cancer is not primarily a disease of excessive cell division, its specialized properties of invasiveness and metastasis and its ability to stimulate a blood supply and stromal reaction require analysis. Knowledge in these areas may suggest specific methods for cancer control or for the synthesis of therapeutic agents. Many planned projects are in progress, some stimulated by the results of empirical chemotherapy trials.

ONCOLYTIC VIRUSES. Viruses often show a predilection for specific tissues, such as the liver, lungs, and central nervous system. Certain viruses have been found to grow in tumor cells and destroy the cells. By growing these viruses in tissue culture of tumor cells and in tumor-bearing animals, attempts are being made to develop strains of viruses selectively injurious to cancer cells. Clinical trials have been conducted with several oncolytic viruses with indifferent results. Despite the theoretical obstacles to success, the potential promise from this approach sustains the continuing investigations.

IMMUNOLOGICAL STUDIES. There is the belief, not definitely supported by valid data, that spontaneous tumors may contain specific antigens foreign to the normal tissues of the host from which they arose. If these antigens produce antibodies in laboratory animals, these antibodies, after suitable purification, can then be given to inhibit tumor growth. If a universal cancer antigen is postulated, these hypothetical antibodies would then be specific for all types of cancer. If the cancer antigen is postulated as appearing incidentally from one of the many cellular mutations leading to cancer, it would be necessary to produce special antibodies for each cancer. It has been suggested that these antibodies be labeled with radioactive isotopes so that the labeled antibody, on localization in the tumor, would irradiate the tumor cells.

ANTIMETABOLITES. The production and study of chemical analogues of essential metabolites and chemical constituents of cells have assumed a major role in cancer chemotherapy. Cancer cells behave differently from normal cells—differences that may be reflected biochemically in a need for unusual metabolic precursors or excessive amounts of normal metabolites for growth and function. Thus the biological peculiarities of the cancer cell may be evidenced by a selective sensitivity to certain antimetabolites. While vitamin and amino acid antagonists are under study, major emphasis is on agents that interfere with nucleic acid synthesis. (This subject is discussed by Hamilton in this issue.)

HORMONAL IMBALANCE. Many cancers are not autonomous but grow optimally under certain physiological conditions in the host. The recognition of important host factors, at least for tumors from organs controlled by the sex hormones, has led to successful measures for modifying their growth. Large doses of androgenic, estrogenic, and adrenal-cortical hormones are often effective, under appropriate conditions, in the treatment of breast and prostatic cancer, and the adrenal steroids are useful in the lymphomas and leukemias. Studies are in progress to discover more active steroid analogues with fewer and less severe side effects; thus meticorten has been proposed as a more satisfactory agent for adrenal-cortical–hormone therapy. Hormonal imbalances are also produced by removal of endocrine glands, such as the gonads, adrenals, and pituitary. The role of the several pituitary hormones, of the thyroid, and of the pancreatic secretions in tumor growth has also come under recent examination. Thus efforts are being made to alter the physiology of the host in a variety of ways in order to make it a less favorable site for the growth of cancer.

POLYFUNCTIONAL ALKYLATING AGENTS. Nitrogen mustard is an alkylating agent in that it introduces alkyl groups in place of hydrogen into organic molecules. Its two reactive ethyleneimine groups are the basis for its toxicological and tumor-inhibiting activity. It is particularly injurious to cells that divide frequently, both normal and neoplastic. It is presumed that the polyfunctional alkylating groups react with many cell components, including nucleoproteins, that are essential for cell reproduction. Their toxicity to the normal marrow prevents adequate dosage in many cases, and there have been many attempts to discover analogues that have a more selective action on tumor cells. While hundreds of polyfunctional alkylating agents have been tested, there is no satisfactory evidence that one has been found with a broader or different spectrum of therapeutic activity or a more selective effect on any particular types of cancer. Bone-marrow depression remains the limiting factor in the use of any of the analogues. Several nitrogen mustard and ethyleneimine analogues have achieved clinical acceptance because they possess some practical advantage in terms of ease of administration or the production of less severe gastrointestinal disturbances. In some patients the selective action of nitrogen mustard can be improved by injecting the drug into the arterial supply to tumor-bearing areas or by giving it intrapleurally or intraperitoneally. Further studies to improve the local effectiveness of this class of compound are desirable.

MISCELLANEOUS COMPOUNDS. A number of miscellaneous drugs with limited tumor-inhibiting activity are being studied. These include urethane, arsenicals, colchicine and related compounds, podophyllin and related substances, and bacterial polysaccharides.

RADIOACTIVE ISOTOPES. The selective deposition of radioactivity in tumor cells is an objective of isotope research. Radioactive iodine has been effective in some cases of thyroid cancer, and radioactive phosphorus is used in diseases of the blood-forming organs. Radioactive gold is given locally to treat pleural and abdominal effusions. The incorporation of radioactive isotopes in organic chemicals that localize in certain forms of cancer would increase their value as therapeutic agents.

RESISTANCE. In many patients drugs temporarily control the growth of neoplastic cells, but ultimately the cells become resistant to further treatment. This may be attributed, in some cases, to progression of the disease. In other instances, however, there is a development of cellular resistance, so that cells at one time susceptible to the action of a drug no longer respond. The development of resistance to the folic acid antagonists by certain strains of mouse leukemia was demonstrated by Burchenal; subsequently this has been shown for many other compounds and with other tumors. Resistance occurs regularly in children with acute leukemia, who respond for a time to one drug and then become refractory to its therapeutic action. The development of drug resistance by neoplastic cells is a great barrier to curative chemotherapy.

COMBINATION THERAPY. Since the beneficial results of chemotherapy are thus only partial and temporary, with resistance ultimately appearing, it is hoped that a combination of several chemotherapeutic agents may produce a longer therapeutic response or actually cure the disease. Transplantable tumors in animals have been used to detect active combinations of drugs, which have then been tested clinically. It is admittedly difficult to evaluate the additional benefits of combination therapy unless the clinical results are much better than those from either drug alone. Thus studies combining estrogens and androgens, nitrogen mustard with cortisone or roentgen rays, synthetic vitamin K (synkavite) with roentgen rays are inconclusive. A recent study with 6-mercaptopurine and azaserine in the treatment of acute leukemia illustrates a combination experiment and demonstrates a slight but definite benefit from combination therapy (Table 1).

It is noted that 6-mercaptopurine, 6-thioguanine, and 6-chloropurine have ap-

TABLE I

Effects of Combination Therapy in Acute Leukemia

	No. children treated	Complete remissions		Partial remissions		Aver. duration, weeks
		No.	%	No.	%	
6-Mercaptopurine (6-MP)	16	7	44	5	31	16
6-Thioguanine (6-TG)	12	7	58	3	25	17
6-Chloropurine (6-CP)	14	7	50	2	14	14
Azaserine	18	0	0	3	17	4
6-MP + azaserine	25	18	72	1	4	23

proximately the same therapeutic activity. Azaserine independently has little effect on acute leukemia. When 6-mercaptopurine and azaserine are combined, an increased number of complete remissions are obtained and these last for a longer period.

Investigative Clinical Chemotherapy

As new drugs, or combinations of drugs, become available as a result of laboratory investigations, they require clinical evaluation to determine their therapeutic effectiveness in cancer in general or in specific forms of cancer in particular. Meticulous trials are essential, because the field is strewn with the wrecks of proposed cures that failed to materialize on subsequent careful analysis. It is apparent that any curative or unusually effective treatment will be readily detected. For the present, however, only compounds of marginal activity are usually available for testing; they may relieve discomfort, reduce the size of large masses, or in some way modify the manifestations or the course of neoplastic disease. It is necessary to know whether a proposed therapeutic agent actually causes an objective change in the disease and, if so, the consistency and duration of the effect and its mechanism of action. Satisfactory answers to these questions require precise and established laboratory and clinical methodology.

Laboratory and Clinical Pharmacology. Adequate pharmacological information on each candidate chemotherapeutic agent is necessary so that proper dosage in man can be estimated and the toxicological hazards appreciated. This requires a toxicological study of the drug in laboratory animals and a preliminary examination of the toxicity of the agent in selected patients with far-advanced cancer. Only after several patients have been treated and a safe maximum dose has been established can more intensive clinical trials be started. It is at this point that many drugs must be discarded because they induce severe injury to the liver, kidneys, skin, central nervous system, etc., and a sufficient dosage cannot be given to affect tumor growth. These trials often require a large amount of a uniform preparation of the test drug. Some of the drugs are very difficult to manufacture in large quantities, and an amount sufficient for a clinical trial can be extremely expensive.

Clinical Oncology. A prerequisite of a proper clinical trial is a thorough knowledge of the natural history of the various forms of cancer, including, for each form, its variations and special complications and its measurable manifestations that can serve as objective criteria of a therapeutic response. By using these criteria against the background of the natural evolution of the disease, the beneficial effects of a therapeutic agent can be determined. This requires careful studies not only on individual patients but also on groups of patients with specific forms of cancer in order to determine the consistency of response. Much effort is being expended to clarify the special features and natural histories of leukemia, Hodgkin's disease, lung cancer, breast cancer, etc., and to establish quantitative objective criteria of response to treatment. Useful criteria will vary, of

SPECIFIC AGENTS USED IN CANCER CHEMOTHERAPY

AGENTS	PRINCIPAL ROUTE OF ADMINIST.	USUAL DOSE	ACUTE TOXIC SIGNS	MAJOR LATE TOXIC MANIFESTATIONS
POLYFUNCTIONAL ALKYLATING AGENTS				
Methylbis(β-chloroethyl)amine HCl (HN2) Mustargen®	I.V.	0.4 mg./Kg. single or divided doses	N. & V.*	Therapeutic doses moderately depress peripheral blood-cell count; excessive doses cause severe bone-marrow depression with leukopenia, thrombocytopenia, and bleeding. Maximum toxicity may occur two or three weeks after last dose. Dosage, therefore, must be carefully controlled.
p-carboxylpropiphenylbis-(β-chloroethyl)amine (CB1348)	Oral	4-8 mg. daily	None	
Triethylenemelamine TEM®	I.V. Oral	0.04 mg./Kg. x 3 20-40 mg. in 1 mo.	Occasional N. & V.*	
triethylenephosphoramide (TEPA)	I.M.	0.2 mg./Kg. x 5	None	
triethylenethiophosphoramide (ThioTEPA)	Oral I.V.	5-10 mg./day 0.2 mg./Kg. x 5	None	
1,4-Dimethanesulfonyloxybutane (GT-41) Myleran®	Oral	2-8 mg./day 150-250 mg./course	None	
ANTIMETABOLITES				
4-Amino-N^{10}-methylpteroyiglutamic acid (Amethopterin) Methotrexate®	Oral	2.5-5.0 mg./day	None	Oral and digestive-tract ulcerations; bone-marrow depression with leukopenia, thrombocytopenia, and bleeding.
4-Aminopteroyiglutamic acid (Aminopterin)	Oral	0.25-1.0 mg./day		
6-Mercaptopurine (6-MP) Purinethol®	Oral	2.5 mg./Kg./day	None	Therapeutic doses usually well tolerated; excessive doses cause bone-marrow depression.
6-thioguanine (6-TG)	Oral	2.5 mg./Kg./day		
6-chloropurine (6-CP)	Oral	20 mg./Kg./day		
Azaserine Seryni®	Oral	2.5 mg./Kg./day (with 6-MP)	None	Sore, red tongue.
STEROID HORMONES				
Androgen Testosterone propionate	I.M.	50-100 mg. 3 x weekly	None	Fluid retention, masculinization.
Methyltestosterone	Oral	100 mg. daily		
Estrogen Diethylstilbestrol	Oral	1-5 mg. 3 x daily	Occasional N. & V.*	Fluid retention, feminization, uterine bleeding.
Ethinyl estradiol	Oral	0.1-1.0 mg. 3 x daily		
Adrenal Cortical Hormones Cortisone® acetate	Oral	50-300 mg. daily	None	Fluid retention, hypertension, diabetes, increased susceptibility to infection.
Hydrocortisone acetate	Oral	50-200 mg. daily		
Meticorten®	Oral	20-100 mg. daily		
Adrenocorticotropic Hormone (ACTH)	I.V. I.M.	25-50 mg. by continuous infusion 10-20 mg. every 3 hr.	None	
RADIOACTIVE ISOTOPES				
Iodine (I^{131})	Oral, I.V.	100-200 mc.	None	Myxedema, bone-marrow depression, renal damage.
Phosphorus (P^{32})	Oral, I.V.	3-7 mc.	None	Bone-marrow depression
Gold (Au^{198})	Intrapleur. Intra-abd.	75 mc. 75 mc.	None	Bone-marrow depression.
MISCELLANEOUS DRUGS				
Urethane	Oral	2-4 gm. daily	N. & V.*	Bone-marrow depression.
Potassium arsenite (Fowler's solution)	Oral	0.2-1 cc. daily	None	Diarrhea, vomiting, skin eruptions.

*N. & V. = Nausea and vomiting

NEOPLASTIC DISEASES RESPONDING TO CHEMOTHERAPY

DIAGNOSES	USEFUL AGENTS	RESULTS
ACUTE LEUKEMIA CHILDREN	AMETHOPTERIN, 6-MP 6-MP + AZASERINE ADRENAL CORTICAL HORMONES	70% bone-marrow improvement; 50% patients live one year or longer.
ADULTS	ADRENAL CORTICAL HORMONES 6-MP, AMETHOPTERIN	15-25% improved for several months or longer.
CHRONIC MYELOCYTIC LEUKEMIA	MYLERAN, TEM, HN2 6-MP P^{32} URETHANE, FOWLER'S SOLUTION	Patients maintained in good condition during major portion of disease; life occasionally prolonged.
CHRONIC LYMPHATIC LEUKEMIA	TEM P^{32} URETHANE ADRENAL CORTICAL HORMONES	Patients maintained in good condition during major portion of disease; life occasionally prolonged.
HODGKIN'S DISEASE	HN2, TEM ADRENAL CORTICAL HORMONES	Occasional favorable response, but no definite prolongation of life.
LYMPHOSARCOMA	HN2, TEM ADRENAL CORTICAL HORMONES	Occasional favorable response, but no definite prolongation of life.
MULTIPLE MYELOMA	URETHANE ADRENAL CORTICAL HORMONES P^{32}, I^{131}	Symptomatic relief in about 50% of cases, and objective hematological improvement in 15%.
POLYCYTHEMIA VERA	P^{32} TEM, HN2	Prolonged clinical remissions, particularly with P^{32}
CARCINOMA OF LUNG	HN2, TEM Au^{198} ADRENAL CORTICAL HORMONES	Brief improvement in about 50% of cases.
CARCINOMA OF OVARY	TEM, HN2 Au^{198}	30 to 50% of cases improved for 1 to 3 months, sometimes longer.
CARCINOMA OF THYROID	I^{131}	Frequent marked improvement in properly selected cases.
CARCINOMA OF BREAST	ESTROGENS, ANDROGENS, ADRENAL CORTICAL HORMONES Au^{198} TEM, HN2	20 to 50% improved by hormonal therapy; life may be prolonged in some cases.
CARCINOMA OF PROSTATE	ESTROGENS Au^{198}	80% of cases respond to hormonal therapy; definite prolongation of life.
MISCELLANEOUS CARCINOMAS AND SARCOMAS	HN2, TEM ADRENAL CORTICAL HORMONES Au^{198}	In rare instances, favorable responses occur.

course, with each type of cancer—for example, the bone marrow in acute leukemia, the serum–acid-phosphatase level in prostatic cancer, and hypercalcuria in patients with osteolytic metastases.

Practical Therapeutic Assessment. The effects of drugs are first explored in patients with far-advanced neoplastic disease no longer responding to conventional therapy. If the drug shows any early promise or is of theoretical interest, and if it is not eliminated by exceptional toxicity, thirty to fifty patients with various forms of cancer are studied, using appropriate objective criteria of response. At this time, if there is no evidence of benefit to the patient, the trial is terminated. If significant improvement is observed in some patients, the series is enlarged, with emphasis, if indicated, on certain forms of cancer. Ordinarily a qualitative assessment of a new agent can be accomplished in six months. In some instances drugs of particular interest receive a clinical assessment simultaneously in several institutions; judgments that are arrived at by several independent groups tend to be sounder.

After a drug is shown to have some intrinsic therapeutic activity, it faces another rigorous test—the evaluation of its clinical usefulness in relation to other available forms of treatment. Drugs may overlap considerably in their spectra of therapeutic activity; it is necessary to determine, for example, whether roentgen rays or nitrogen mustard is more useful in certain situations, whether thio-TEPA has any advantage over TEM, or whether meticorten is superior to cortisone in the treatment of acute leukemia.

By putting new forms of treatment through this sequence of clinical study, those that are worthy will be established as such; and the failures will be self-evident, either as a result of proper testing or by default, if the proponent refuses to subject his form of treatment to the rigors of an established scientific methodology.

Current Clinical Chemotherapy

There are a number of drugs useful in treating certain forms of neoplastic disease. These drugs are not curative but they can temporarily relieve some of the manifestations of cancer, improve the patient's situation, and sometimes prolong life. These agents have specific effects on cancer, in the sense that they modify the growth of cancer in some manner, in contrast to the important, but nonspecific, supportive agents, such as analgesics and antibiotics. The indications for these specific drugs cannot be considered here in detail, and reference will be made to some general reviews. The outlines on pages 170 and 171 condense the basic information on the pharmacology of the drugs, their indications in various forms of cancer, and general benefits to be expected from their use. It is emphasized that roentgen-ray therapy is the most important palliative method available and should be used when indicated. Chemotherapy is not to be regarded as a substitute for roentgen-ray therapy.

Conclusions

The chemotherapy of cancer will continue to be a major area of biological and medical research until chemicals are found that control the growth of, or obliterate, all forms of the disease. Thus far, as a result of recent efforts, drugs have been introduced into clinical practice that exert regular therapeutic effects on some forms of neoplastic disease. They are useful in the management of many patients with nonresectable or disseminated cancer.

A number of indirect benefits to the cancer patient have accrued from the work in chemotherapy. It has stimulated active concern for patients with advanced cancer, and, as a result, these patients are better cared for, and all the resources of medicine are being brought to bear on their individual problems. It has provided productive opportunities for clinical re-

search, particularly in those patients who demand active therapy during the course of a relentless disease. It has kept patients and their families hopeful and cheered by the fact that something is being done. It has trained physicians to regard disseminated cancer as another form of chronic disease and impressed on them the therapeutic rewards from the skilled management of their patients through a sometimes rocky, progressive, and often protracted clinical course.

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Specific Agents Used in Cancer Chemotherapy

Neoplastic Diseases Responding to Chemotherapy

A print of the tabulations on pages 170 and 171, suitable for framing, can be obtained from:

Mr. Russell Gray Smith
Distribution Manager
American Cancer Society, Inc.
521 West 57th Street
New York 19, New York

Practical Aspects of Chemotherapy of Leukemia and Related Disorders

A Clinic in the Department of Medicine, University of Utah College of Medicine, at the Salt Lake County General Hospital

DR. WINTROBE: During the past ten to twelve years, a variety of chemical agents for the treatment of neoplastic disorders has become available to the medical profession. We should like to illustrate a practical approach to the clinical application of several of the more useful of these drugs.

Case 1

A 5-year-old boy with acute lymphoblastic leukemia of recent onset was hospitalized because of epistaxis and fever. He was febrile and pale. Ecchymoses, petechiae, cervical and axillary adenopathy, hepatosplenomegaly, and sternal tenderness were present. Bleeding was controlled by nasal packing. Blood cultures and urine were negative. Cortisone, 25 mg. by mouth every six hours, was started together with potassium chloride and a low salt diet. He was discharged five days later on this regimen.

DR. WINTROBE: Would you discuss the choice of cortisone in this patient?

DR. ALTMAN: In lymphoblastic leukemia, we initiate therapy with cortisone, since it induces the highest percentage of complete remissions and the remission occurs in a shorter period and in a more predictable fashion than after the use of any other agent. Fever and bleeding disappear promptly. The lymphoblasts disappear from the blood, resulting in a profound leukopenia during the second week of therapy. Hemoglobin concentration, platelet count, and white-blood-cell count return to normal by the end of the fourth week. Leukocytosis owing to myeloid elements may develop temporarily. Organ enlargement and sternal tenderness regress with hematological improvement. If a complicating infection had been found, we would have started therapy with amethopterin or 6-mercaptopurine.

DR. WINTROBE: How do you select an adequate dose of cortisone?

DR. ALTMAN: One hundred to 200 mg. a day is the dose that usually will produce a remission. Hydrocortisone is also effective. Limited experience suggests that the same may be true of meticorten.

DR. WINTROBE: What is your plan for future care?

DR. ALTMAN: Since maintenance on cortisone is ineffective, amethopterin will be started when maximum improvement has been achieved, generally in four or five weeks. The dose of cortisone will be reduced to zero over a ten-day period. Generally, 1.25 to 2.5 mg. of amethopterin are sufficient to maintain a remission. When relapse occurs, amethopterin will be increased as necessary. When refractoriness develops, we will switch to 6-mercaptopurine, 2.5 mg. per Kg. per day, in intermittent courses.

DR. WINTROBE: Bone-marrow aspirations are not necessary for routine diagnosis or care of the patient. They should be reserved for the suspected case of aleukemic leukemia or during the course of therapy when one is faced with the dilemma of deciding between a drug or a disease-induced pancytopenia. This does not become a problem during cortisone therapy. We allow our patients as normal a life as possible. During remissions, we see them at two- to three-week intervals; during relapses, as often as every three to seven days. Hospitalization is reserved for problems of infection and bleeding and for transfusions. Transfusions are withheld unless uncontrollable hemorrhage or anemia of sufficient severity to cause symptoms is encountered. We prefer to await the spontaneous rise in hemoglobin incident to successful chemotherapy.

Case 2

A 42-year-old white woman was found to have "too many white cells" on routine blood examination after a foot injury. When the patient was seen here, the diagnosis of chronic myelocytic leukemia was made. In retrospect, she admitted minimal weakness, fatigue, and occasional headaches in the preceding eight months.

Physical examination revealed slight pallor, moderate mid-sternal tenderness, slight hepatomegaly, and marked splenomegaly. A volume of packed red cells of 34 ml. per 100 ml. blood, increased buffy layer, 333,500 leukocytes per cu. mm., the typical "shift to the left," and increased platelets were found.

Myleran, 4 mg. daily, was given and the patient was instructed to return in four weeks for follow-up evaluation.

DR. WINTROBE: Why was myleran chosen?

DR. WALTER: Myleran is an orally administered, safe, effective agent, the use of which is not associated with gastrointestinal side effects.

DR. WINTROBE: How do you manage the patient on myleran therapy?

DR. WALTER: Therapy will be continued until the leukocyte count is reduced to less than 10,000 per cu. mm., usually two to three months. White-blood-cell counts will be performed at monthly intervals and more often as we approach this objective. Blood transfusions will not be necessary, for an appreciable hemoglobin response will occur within thirty days.

DR. WINTROBE: Is the daily dose of myleran 4 mg. in all patients?

DR. WALTER: The dose is 0.06 mg. per Kg., usually 4 to 6 mg. daily. When thrombocytopenia exists, somewhat smaller doses may be used.

DR. WINTROBE: Will future plans include this agent?

DR. WALTER: To date we have not noted refractoriness to myleran, though we have used it as many as four times in the same patient. Currently we use myleran in intermittent courses whenever relapse occurs.

DR. WINTROBE: Myleran is effective only in chronic myelocytic leukemia and is of no value in the terminal acute phase. Experience to date suggests that this drug is at least as effective as roentgen-ray therapy. We believe the ease of administration and lack of side effects make it the treatment of choice. A word of caution: myleran is capable of producing thrombocytopenia and even bone-marrow hypoplasia.

Case 3

A 24-year-old white man was admitted to the hospital complaining of fatigue, weakness, weight loss, intermittent febrile episodes, and generalized pruritus of nine months' duration. Physical examination

revealed moderate lymph-node enlargement in several regions. A complete blood count showed moderate neutrophilia, lymphopenia, and slight thrombocytosis. The chest roentgenogram showed "possible widening of the superior mediastinum." Lymph-node biopsy established the diagnosis of Hodgkin's disease.

DR. WINTROBE: Now that the diagnosis is established, what are your plans for treatment?

DR. LEVINSON: This patient will be treated intravenously with 0.6 mg. per Kg. of nitrogen mustard (HN2) over a two- or three-day period. Future courses of therapy will depend upon his response.

DR. WINTROBE: Why was HN2 chosen rather than radiation therapy or triethylenemelamine (TEM)?

DR. LEVINSON: Since expected beneficial effects are similar but the morbidity and time required for therapy are less with HN2 than with roentgen-ray therapy, we prefer the former agent. Also, the disease is widespread and mustard will exert its influence throughout the body, obviating the necessity for multiple-port roentgen-ray exposure. As far as TEM is concerned, the effects are less predictable than with HN2 because of variability in intestinal absorption of this orally administered agent.

DR. WINTROBE: How soon after mustard therapy do you want to see this patient again?

DR. LEVINSON: Constitutional symptoms and organ enlargement respond rapidly, but the maximum effect is not evident for two to three weeks. Hematological recovery occurs by the fourth to sixth week. This patient will be seen at that time and completely re-evaluated. If evidence of disease exists, further therapy will be given. If not, he will be followed at two- to three-month intervals.

DR. WINTROBE: Should you decide to administer more HN2, what guide do you use for dosage?

DR. LEVINSON: The dose depends upon the extent of tissue involved; the presence or absence of constitutional manifestations; the presence or absence of anemia, leukopenia, and thrombocytopenia; and the response to previous therapy. The dose may be 0.2 to 0.8 mg. per Kg.

DR. WINTROBE: The profound effects of mustard, as well as other therapeutic agents for this disease, on the hematopoietic system must be respected. Aplasia of the bone marrow may be induced with excessive dosage. It is not yet established clearly that patients treated with these agents survive any longer than untreated patients. Nevertheless, there is little doubt that chemotherapy adds materially to the sense of well-being, productivity, and happiness of the patient. It may be stated also that there is no competition between roentgen-ray therapy and chemotherapy. Both forms of treatment have an important place in the management of Hodgkin's disease.

ORS' DILEMMAS

Q *Careful examination of the head and neck has failed to reveal any evidence of a malignant process in a 42-year-old man whose only complaint is of persistent enlargement of the nodes in the right cervical chain. There are no palpable enlarged nodes on the left and physical examination otherwise is unremarkable, as is a chest roentgenogram. I am concerned however that this asymmetrical enlargement of the cervical nodes may represent evidence of an "occult" malignant process.*

A Asymmetrical enlargement of the cervical lymph nodes in an adult is almost always associated with a malignant process. Most often it is due to metastases from a primary lesion in the mouth or pharynx, and occasionally such enlargement represents metastases from a viscus below the level of the clavicle. Further and repeated careful examinations should be undertaken in search for the primary tumor, since not infrequently these primaries are very small and obscure and the metastases are the first symptoms of the underlying disease. Although Hodgkin's disease and lymphosarcoma are generally thought of as involving multiple nodal areas and, when cervical nodes are involved, as appearing bilaterally, the fact is that the initial expression of malignant lymphoma may be confined to one side. A single nodal area is less likely to be enlarged in leukemia. Of course, much of the uncertainty in this case can be dispelled by a biopsy, removing an entire node rather than wedge sectioning.

Q *I have as a patient a woman, 49 years old, who has had a watery discharge from the left nipple intermittently for the past four months. It has become more persistent recently. There has been no bleeding, and there are no lumps palpable in the breast or axilla. Should a biopsy be performed?*

A Watery nipple discharge is usually associated with an intraductal papilloma that may be malignant and that, if not, is potentially so. Any nipple discharge not normally associated with lactation should be investigated surgically. If papillomas of the breast are multiple, partial or simple mastectomy should be considered; if the papilloma is solitary and can be accurately localized, excision of the duct is the usual procedure. Needless to say, radical mastectomy should be performed if the pathological diagnosis indicates cancer.

Q *A 56-year-old man who had complained of severe gastric symptoms was shown by roentgen-ray examination to have a gastric ulcer situated on the lesser curvature. Conservative medical therapy was instituted and the patient's symptoms were relieved. Repeat roentgen-ray examination after one month was entirely negative. He has now, four months later, had a recurrence of his former symptoms, and new roentgenograms show a recurrence of the ulceration. Is surgery indicated?*

A Yes. Gastric ulceration that recurs fol-

lowing adequate conservative medical therapy is a strong indication for surgical intervention.

Q *A patient of mine who had a basal-cell carcinoma on his forehead was treated successfully with radiation two years ago. He is now 60 years of age. At the site of treatment there is now an atrophic, telangiectatic area. This patient plays a good deal of golf and has asked me whether the treated area can safely be exposed to the rays of the sun and whether it is probable that additional skin cancers will develop in other exposed areas of skin.*

A Unnecessary exposure to the sun should be avoided, and this man should be advised of the possibility that other skin cancers may develop. These should be treated promptly to obtain the same good result achieved in the management of the lesion on his forehead.

Q *What is the basis for advocating hypophysectomy in the treatment of cancer?*

A Secretion of the hypophysis is essential for the production of hormones by the ovaries, testes, adrenals, and thyroid. Without this stimulus these glands will cease to function, that is, to produce estrogens, androgens, adrenal hormones, and thyroxin. Since the growth of cancer of the breast and of the prostate is dependent upon the presence of estrogens and androgens respectively, the lack of these substances will retard the growth of these endocrine-dependent tumors — hence the rationale of castration as a treatment of certain cancers. But estrogens and androgens are also produced by the adrenals, so if total sex-hormone deprivation is sought, they must be removed also. It has also been considered that breast and prostate cancer might be dependent upon pituitary hormone for growth. Thus hypophysectomy would remove the source of these hormones as well as eliminate the sex hormones.

Q *How long does it take for gastric cancer to become clinically manifest?*

A This question has not been settled with certainty. Present opinion, however, is that the interval between the onset of the disease and the first symptoms probably averages about two years, depending, of course, on the location of the cancer and its biological aggressiveness. When the tumor is located near either orifice of the stomach, symptoms probably occur much earlier, and perhaps it is because cancer in the prepyloric area causes earlier symptoms than cancer of the fundus that most cures of gastric cancer are obtained in patients whose disease is so situated as to cause early symptoms.

Q *Is it desirable to remove so-called senile keratoses as a prophylactic measure for the prevention of skin cancer?*

A It is always preferable to treat a benign lesion rather than to postpone treatment until a malignant lesion develops. Both basal-cell and squamous carcinoma are known to develop in senile keratoses, and such lesions, especially when they occur on exposed skin surfaces or surfaces subjected to irritation, should be removed surgically or treated with electrodesiccation, carbon dioxide, or radiation therapy.

new developments in cancer

Prostate Test? . . .

Large doses of cortisone greatly increased the 17-ketosteroid output in six prostatic-cancer patients under observation at Yale. The same treatment had little or no effect on the excretory pattern of eight normal persons.

This finding has caused Joseph E. Sokal and others at the Yale University School of Medicine to explore the possibility that the phenomenon might have clinical value as a "cancer test."

Three of four persons with nonprostatic cancers showed the response demonstrated by the prostatic-cancer cases.

Good and Bad Anthrax . . .

When the bacterium that causes anthrax is transformed from a harmless organism into a killer of cattle and man, its DNA (desoxyribosenucleic acid) content increases considerably. Robert P. Williams of Baylor is investigating this phenomenon. One possibility is that a virus, behaving as a newly acquired gene, endows the anthrax cells with toxin- synthesizing properties. Anthrax, once a frequent killer of American men who failed to sterilize their shaving brushes (it exists on hides from which pig bristles are obtained), has been seen rarely since sterilization measures were enforced.

Tomorrow's Medicine . . .

A group of scientists at the University of Pennsylvania are producing in test tubes some of life's most vital compounds. Moreover, they are doing it without the aid of cells or even cell particles. They do it with soluble enzymes. This is basic research, at present without clinical implications, but it is of the sort that may make possible medical miracles of the future.

Samuel Gurin and D. Wright Wilson are using the enzymes and the compounds upon which they work to build up and tear down specific fats, proteins, hormones, and nucleic acids. Already they have traced much of the metabolic process by which acetic acid, with its two carbon atoms, is built into cholesterol, which contains twenty-seven carbon atoms. They also are studying how the adrenals chop a six-carbon chunk (isocaproic acid) off the cholesterol molecule to produce twenty-one–carbon steroid hormones.

Among the conditions that stand to be explained by such work as this are the failure to produce fat in diabetes, hormone abnormalities in a number of physical and mental diseases, the piling up of choles-

terol in atherosclerosis, and even the vagaries of nucleic acid metabolism in some genetic conditions.

Liver and Poisoning . . .

In hemochromatosis, lead poisoning, and some other kinds of poisoning—sometimes forerunners of liver cancer—liver cells lose ability to regulate their intake of heavy metals. This finding was made by Paul D. Saltman and Edward Butt of the University of Southern California and Los Angeles County Hospital respectively. Healthy liver cells have about one hundred charged iron particles inside them for every thirty particles on the outside. In lead poisoning, liver cells contain 100 times the normal amount of iron, ten times that of lead, and four times that of molybdenum. Similarly abnormal ratios are observed in several other forms of poisoning. The investigators feel that poisoning destroys a pumping mechanism (possibly enzymatic) in the cell membrane that regulates the intake of heavy metals and that the metals are sopped up as though by a sponge. They have observed that the poisons act upon compounds containing sulfhydryl (SH) groups, and they are attempting to restore the balance in sick cells by feeding them SH-containing compounds.

Intersex Psychology . . .

Pediatricians and psychiatrists at Johns Hopkins Hospital have concluded a study of the problems of hermaphrodites with these recommendations:

1. When sex-organ deformities are recognized at birth, medical and hormonal studies should be made as soon as possible to determine whether or not there is an adrenal disorder requiring cortisone treatment.

2. In cases in which the deformities are not due to an adrenal disorder, the appearance of the external sex organs should be one of the major guides in deciding the sex in which the child should be reared, and surgery should be performed to prepare the patient to live a normal adult sexual life in the sex of rearing.

3. When hermaphroditic signs are not properly diagnosed until later childhood, doctors and parents should be guided by the child's indelible thought habits and personal convictions of his or her gender, as appraised by a specialist in psychiatric medicine.

4. After the early infancy periods, changes of sex assignment should be avoided at almost any cost.

The studies, conducted by Lawson Wilkins, John L. and Joan G. Hampson, and John Money, used as four criteria for the determination of sex: genetic or chromosomal composition, external sex organs, sex endocrine organs, and sex "conviction." Sex conviction—the feeling of maleness or femaleness, which is established usually within the first eighteen months—was regarded as more important than any other criteria in assigning sex to hermaphrodites more than 3 years old.

Delay in Fertilization . . .

The metabolism of embryos is profoundly affected by the time lapse between the release of the ovum from the follicle and the moment of fertilization. This has been established in marine forms of life by Hans G. Borei of the University of Pennsylvania. Normally, oxygen consumption by ova decreases gradually from the time the egg is released until fertilization brings about a sharp rise. As this interval increases, the change-over from oxidative to fermentative metabolism becomes more and more drastic. Investigation by Emil Witschi of the State University of Iowa has shown that delayed fertilization frequently produces monsters—and maximum delay produces cancer-riddled offspring.

that the white cells of cancer patients (thirty-one with various solid tumors and thirty-two leukemics) contain 4.5 times as much glutamic acid dehydrogenase (GAD) as do the white cells of nineteen normal people. GAD levels were very consistent in all normals, varying by not more than 2 or 3 per cent; and they were equally consistent in all but one cancer patient. The single exception, for some unfathomed reason, had a GAD level lower than normals. The investigator does not feel that this amounts to a blood test. He is more interested in the cause of the variance, which, tentatively, he attributes to the rapid protein turnover in cancer patients. He feels that he may find equally startling differences in other enzyme levels in the two groups.

Kotin and Falk (U. S. Calif.) have reported that aliphatic hydrocarbons extracted from the atmosphere and painted on mouse skins three times a week produced two cancers and five papillomas among thirty-five mice in fourteen months. The same team reported that, at autopsy, the average city dweller shows only about 1 gm. of soot in his lungs. No carcinogenic aromatic hydrocarbons were found in the soot.

Goldie and associates (Meharry) have come to the conclusion that it is the site, not the size, of the tumor that determines how long the cancer patient lives. They have shown that, by suppressing metastases from primary tumors implanted in the mouse thigh or peritoneal cavity, death can be delayed by a considerable period. A tiny metastatic lesion to the brain, lung, or other vital organ, on the other hand, may bring about the animal's death while the primary tumor is still small. Goldie feels that cancer kills chiefly (1) by hemorrhage and (2) by destroying the function of such vital organs as liver or spleen.

Employing a wide range of ingenious techniques, including the reduction of solid tumors to single cells that grow suspended in ascitic fluid in the peritoneal cavity, the investigators have laid an impressive basis for several theories. They also have used extensively a method for finding occult metastases -- they mince organs and inject the brei of each organ into another mouse. If metastatic cells are in the organ, the new host develops a tumor quite rapidly.

In one series of experiments they implanted tumors in mice and treated half the animals with cortisone. These mice developed tumors that showed the presence and site of

metastases. But when the organs of these and the organs of the others that had not been treated with cortisone were minced and injected into mice, both the treated and untreated animals showed pretty much the same number of metastases. Goldie has concluded that cortisone does not cause metastatic spread of disease but merely makes established metastatic colonies grow faster.

They also found that radioactive isotopes, injected intravenously or intraperitoneally, have a substantial destructive effect on metastatic tumors. When tumors from animals that had been treated with radioactive iodine, gold, or chromium were transplanted to new hosts, many would not grow. Tumors from mice untreated with isotopes grew readily and rapidly in new hosts. The group found that the isotopes, in the doses used, had little or no ill effect on normal cells. Macrophages ingested the particles without much apparent damage. These and similar results by other investigators have indicated that cancer patients, at the time of operation and later, should be treated with radioactive isotopes as a prophylactic measure against metastases and disease recurrence.

A few years ago Brown and Price (U. of Wis.) gave themselves this problem: "Everybody knows that dye workers exposed to aromatic amines (like beta-naphthylamine) frequently develop bladder cancer. But so do many others who are not exposed to this type of compound. Why?" They have turned up this answer: Tryptophane yields five aromatic amines metabolically. These five substances have been found in the urine of individuals both with and without bladder cancer. When bladder-cancer patients were given 2 gm. of tryptophane, the urinary levels of three of the five metabolites increased severalfold; in normal persons, the tryptophane brought only a slight increase in urinary metabolites. Therefore, it may be that some become bladder-cancer victims because they are unable to handle increased amounts of tryptophane in the normal manner.

COMING MEDICAL MEETINGS

Date	Meeting	City	Place
1955			
Oct. 9-12	California Academy of General Practice Seventh Annual Scientific Assembly	San Francisco	Sheraton-Palace Hotel
Oct. 10-15	American Society of Clinical Pathologists	Chicago	Drake Hotel
Oct. 10-21	Graduate Fortnight of the New York Academy of Medicine	New York City	Hosack Hall
Oct. 17-20	American Dental Association	San Francisco	Civic Auditorium
Oct. 22-26	American Heart Association	New Orleans	
Oct. 22-26	Pan American Congress of International College of Surgeons	Mendoza City, Argentina	
Oct. 24-29	American College of Gastroenterology	Chicago	
Oct. 30-Nov. 4	American College of Surgeons	Chicago	Conrad Hilton Hotel
Nov. 1-3	International Symposium on Enzymes: Unit of Biological Structure and Function	Detroit	Henry Ford Hospital
Nov. 7-9	Association of Military Surgeons of the United States	Washington, D. C.	Hotel Statler
Nov. 7-12	International General Medical Congress	Rosario, Argentina	University of Rosario Medical College
Nov. 11-12	Third Annual Meeting, Inter-Society Cytology Council	Cleveland, Ohio	Statler Hotel
Nov. 14-17	Southern Medical Association	Houston, Texas	
Nov. 14-17	40th Assembly, Interstate Postgraduate Medical Association	Milwaukee	Municipal Auditorium
Nov. 14-18	American Public Health Association	Kansas City, Mo.	Municipal Auditorium
Nov. 29-Dec. 2	Clinical Meeting, American Medical Association	Boston	Mechanics Hall
Dec. 3-8	American Academy of Dermatology and Syphilology	Chicago	
Dec. 11-16	Radiological Society of North America	Chicago	
Dec. 12-14	American Academy of Obstetrics and Gynecology	Chicago	Conrad Hilton Hotel
Dec. 26-31	American Association for the Advancement of Science	Atlanta, Ga.	

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